PATHOGENIC EFFECTS OF THE THERMAL FACTOR

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16. Abstract

This chapter contains articles on the following subjects: the pathological physiology and the pathogenesis of the initial period of burn disease, overheating, cold trauma, and hypothermia.

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PATHOGENIC EFFECTS OF THE THERMAL FACTOR

PATHOLOGICAL PHYSIOLOGY AND THE PATHOGENESIS OF THE INITIAL PERIOD OF BURN DISEASE

N. A. Fedorov[1]

The problem of thermal burns has acquired considerable importance in recent /180* years. According to the data of the World Health Organization (WHO), traumas resulting from accidents held first place as a cause of death in technically developed nations in recent years. According to the data from various authors, burns made up 5.2-10% of these traumas. In the USA, the number of persons injured by burns each year has reached 900,000 (T. Ya. Ar'yev, 1966), with 70,000 burn victims being hospitalized. At the present time, about 12,000 people die from burns every year in the USA. The total number of individuals admitted to medical centers for treatment of burns in our country has reached 0.3-0.9% of the total population each year (data for Kiev, Vinnitsa, Kaunas and Riga for 1958; T. Ya. Ar'yev, 1966).

The timeliness of the problem is also due to its military significance. In the explosion of the two atomic bombs above the Japanese cities of Hiroshima and Nagasaki, approximately 100,000 persons suffered burns. The cause of death under these conditions in almost half the cases was burns (Artz, Reiss, 1958).

Particular attention is attached to the combined thermal-mechanical, thermal--radiation and thermal-chemical injuries which inevitably develop as the result of nuclear explosions and fires.

An important role in thanathogenesis in burns is played by factors which cause injury to the resporatory pathways. Such injuries have been observed in recent years in 40% of those dying from burns (V. M. Pinchuk, 1960). The principal cause of injury to the respiratory pathways is breathing of tongues of flame and smoke.

The pathology of burns is not limited to local changes in the tissues; extensive and deep burns cause diverse, prolonged and serious functional disruptions of the internal organs and systems of the organism, and therefore the concept of "burn disease" has become increasingly popular in recent years. The term "burn disease" was first used by Wilson (1938). This term emphasizes that burns must be viewed as a disease of the organism as a whole and not as a local thermal injury to the cutaneous coverings.

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*Numbers in the margin indicate pagination in the foreign text.

The concept of periodization of burn disease has developed. The majority of pathophysiologists and clinicians distinguish the following periods: burn shock, toxemia, infection, exhaustion and recovery. Some authors feel that the /181
second and third periods must be viewed as one and refer to it as infectious--toxic. This periodization is arbitrary to a large extent. Shock does not always have a clinical pathophysiological manifestation. Toxemia arises during the first hours following the burn; burn infection is also observed during the first 24 hours, i.e., during the period of burn shock. Exhaustion begins to develop during the very first days of the disease if the burns are deep and extensive.

Pathophysiologists and clinicians have undertaken a careful and comprehensive study of the significance of the depth of injury to the skin and subjacent tissues in the pathogenesis of thermal burns. It has been found that the seriousness of burn shock and subsequent autointoxication are determined not by the total area of the injury, as was thought until recently, but the surface area of the burn, where the entire thickness of the skin is necrotized. It is specifically the area of deep burns which largely determines the fate of the victim (T. Ya. Ar'yev, 1966). Such basic symptoms of burn shock as thickening of the blood, oliguria, damage to the liver and so forth can occur in the case of superficial (although extensive) burns.

Bull and Fischer (1954) consider a superficial burn to be equivalent to four times the minimum area of a deep burn, while other authors (Artz, Reiss, 1958; Frank, 1960) reduce this equivalency to 2-3. The relationship which has been observed between the area of a deep burn and the severity of the pathological reaction is so striking that on the basis of a qualitative evaluation of this reaction it has been possible to develop a method for the determination of the area of deep burns. Ye. V. Gubler (1965), on the basis of a method of computer diagnosis employed only 10-30 hours following a burn, on the basis of indications regarding the pulse, body temperature, arterial pressure and number of leucocytes, as well as a consideration of the total surface of the burn, was able to determine in the majority of patients that deep-burn area which is significant for the selection of methods of treatment and prognosis of the severity of the course of burn disease.

In conjunction with the above, it becomes clear that flame is primary among those thermal agents which cause the most severe injuries in man. Severe burns in man are caused by napalm (V. A. Dolinin, 1960), due to intensive and deep burning of the tissues as well as prolonged hyperthermia. Shock following burning by hot water is encountered extremely rarely (T. Ya. Ar'yev, 1966). As indicated by experiments, this difference is explained by the fact that there is a deep heating of the tissues with necrosis in burns caused by flame, while the brief action of hot water heats only the superficial layers of the skin.

Therefore, we can consider established the view that deep injury to the skin is the primary and most important factor in the pathogenesis of burn disease as a whole. The mechanism of the pathogenetic influence of thermally injured skin on the diverse functional activities of the organism remains little studied, however, and constitutes a very important problem for the pathological physiology of burns.

It is important to note that the actual duration of hyperthermia of the tissues is usually much longer than the time of action of the thermal agent itself. In burns by water and steam, this increase is relatively low (2-3 times). In the case of flame burns, especially burning of clothing, napalm burns and so forth it is increased by 5-7 times (N. I. Kochetygov, V. L. Belyanin, 1964). This is precisely why burns caused by water are superficial and those caused by flames are deep. From this we can understand the advisability of local cooling in the vicinity of the burn, which considerably cuts down the period of post-burn overheating of the tissues, resulting in a decrease of the depth of necrosis. /182

On the basis of all of these data, N. I. Kochetygov developed more complete models of burns in an experiment. Accordingly, he characterizes not only the area of the burn but its depth.

Thus, for example, it has been established that an increase in the temperature on the internal surface of the skin due to a burn to 55-60° (needle thermocouples were used for measurement) causes necrosis of the total thickness of the skin without damage to subjacent tissues (degree of burn: IIIb). If such a burn covers 15-20% of the surface of the body, animals which are kept in a warm place for the first 24 hours usually do not die of shock. One can see in them all of the periods of burn disease (with intensive care and reinforced diet). If a IIIb-degree burn covers 30-40% of the body surface, the majority of animals will die in a state of shock which, as is the case in the clinic, develops in the course of 12 or 14 to 48 hours.

Burn Shock

Burn shock has been conditionally divided into erectile and torpid stages. The erectile period is characterized by general irritation of the burned victim, increased arterial pressure, speeding up of the respiration, increased gas exchange, and increased content of adrenaloid substances in the blood. Some researchers do not isolate the erectile phase (T. Ya. Ar'yev, 1966; Ye. V. Gubler, 1965), since the phenomena of excitation, increased energy exchange and other phenomena of the erectile phase are frequently observed during all periods of shock.

The pathological physiology of torpid burn shock consists of such functional disturbances as cardiovascular insufficiency, decreased volume of circulating blood, hemoconcentration, acute renal insufficiency, oliguria, disruption of water-electrolyte exchange, as well as profound disturbances of the intercurrent nitrogen metabolism, liver damage, and blockage of natural protective factors.

Cardiovascular system. A characteristic feature of burn shock is the relative stability of the arterial pressure. According to our observations (N. A. Fedorov and V. B. Troitskiy, 1965; N. A. Fedorov, S. V. Skurkovich, 1955), in dogs with lethal burns caused by flame (the area of deep skin injury was 20-40%) the decrease in maximum arterial pressure does not exceed 20-30% of the original level and hypotonia is observed only in the terminal period. There is a regular drop in the pulse pressure as a result of an increase in the

minimum pressure or a drop in the maximum pressure. On the basis of the clinical data, although they are contradictory, the majority of authors conclude that the index of arterial pressure in burns cannot be viewed as a criterion for the severity of burns. Sevitt (1954, 1957) views a decrease in the arterial pressure as a late, prognostically unfavorable sign indicating a pronounced degree of disruption of the coronary and cerebral circulation, unavoidably causing death. T. Ya. Ar'yev (1966) also concludes that even a normal arterial pressure level does not exclude the possibility of burn shock with a lethal outcome.

All of the above indicates a theoretical difference between burn shock and traumatic shock.

The resistance of the arterial pressure in thermal injury is explained by the increase in the vascular tone, as indicated by the resistography method in /183
the renal, mesenteric and femoral arteries in seriously burned dogs (V. B. Troitskiy, 1967).

The phenomenon of vasoconstriction in burns was also observed by many authors in the clinic. Abell and Page (1943), in the case of 9 patients with serious burns, observed an increase in the general blood flow resistance by a factor of two, and explains this phenomenon by generalized vasoconstriction. Increased viscosity of the blood, which necessarily accompanies burns, is of a secondary significance in the opinion of these authors. Using the method of vital microscopy, the authors observed significant constriction of the lumina of the minor arteries after only 10-20 minutes had elapsed following the burning of the rear extremities of dogs and cats with boiling water; the blood flow in the arterial and venous vessels was significantly reduced, even resulting in stasis. Prinzmetal et al. (1945-1948) and Simonart (1958) observed general dilation of the capillaries of the internal organs only a few minutes after a burn.

In addition to the contraction of the arterial vessels and the dilation of the capillary bed, considerable significance in the mechanism of the increased total blood flow resistance in burn victims must be assigned to the phenomenon of aggregation of erythrocytes, which naturally leads to a change in the rheological conditions of the blood circulation (Knisely, 1962). Particular attention must be paid to the catecholamines and corticosteroids. Birke et al. (1957) and Chester and Harrison (1967) observed that the urine of burn victims showed increased adrenaline, and to a large extent noradrenaline, depending on the severity of the burns. At the same time, the adrenals and sympathetic ganglia showed a sharp decrease in the catecholamine content.

A number of authors have observed an increase in the activity of the hypophyseal-adrenal system, as indicated by the increase in the 17-hydrocorticosteroid content in the blood (Hime, 1955; Pekkarinen, 1960). Markley (1960) feels that burns over 25-50% of the surface of the body cause maximum stimulation of the glucocorticoid function of the adrenals for several days following a burn.

Hence, it may be assumed that burn trauma is accompanied by the excretion into the blood of a large quantity of catecholamines which produce and maintain a generalized spasm of the arterial vessels. Hydration of the organism by glucocorticoids in the initial period of the burn also may promote an increase in the resistance of the arterial vessels, inasmuch as these hormones potentiate the action of the pressor substances and increase the reactivity of the vessels to the pressor impulses from the sympathetic nervous system (Levin, 1951). Agglutination of the formed elements of the blood causes precipitation of the conglomerates in the small arteries, capillaries and venules, which can impede blood flow and even stop it completely.

Hence, we can conclude that a burn victim undergoes generalized spasms of the arterial vessels, with the exception of the coronary and cerebral vessels. At the same time, the c pillary bed dilates and its capacity increases; this naturally leads to pathological deposition of blood and decreased venous return.

The problem of the mechanism of burn vasoconstriction has been insufficiently clarified. Sevitt (1957), for example, concludes that there is a dual mechanism for this phenomenon -- nervous and humoral. In response to oligemia, via a reflex arc composed of the aorta and the carotid sinus, activation of the vasomotor center takes place and general contraction of the arterial vessels occurs through the sympathetic nervous system. We cannot exclude the possibility of involvement of the renin-angiotensin system in the mechanism of the /184
increased resistance of the vessels, inasmuch as burns are followed by an increased formation of renin in the kidneys with subsequent enrichment of the blood with angiotensin 1 and 2 (Shir, 1952). On the basis of our data it may be suggested that the mechanism of the burn arterial spasm has a primarily humoral nature. In fact, total denervation of the renal and mesenteric arteries does not prevent a sharp increase in the resistance of these vessels following thermal trauma.

Volume of circulating blood. The decrease in the volume of circulating blood and hemoconcentration are reliable and characteristic symptoms of burn shock. Gilmore and Fossard (1960), using radioiodine, observed a decrease in the volume of circulating blood by up to 50% in extensive burns to human beings. N. I. Kochetygov (1962) and P. M. Fedonyuk (1963) observed a similar decrease in the volume of circulating blood by 50% following serious burns in animals. Such a significant reduction of the circulating blood naturally could give rise to pronounced hemodynamic disturbances; this has enabled several authors to consider burn shock oligemic. The degree of the decrease in circulating blood depends upon the nature of the thermal agent causing the shock. In severe flame burns in dogs, the volume of circulating blood decreases by as much as 30% of the original level; after 4-8 hours, normalization occurs (V. B. Troitskiy, 1967). At the same time, in the case of burns from boiling water, there is a much more pronounced hypovolemia -- up to 50% (V. B. Lemus, 1962, 1965).

The mechanism of burn oligemia is complicated and includes the following components: 1) plasma loss (white blood flow); 2) erythrodiuresis; 3) pathological deposition of the blood in the capillaries.

The significance of plasma loss in the pathogenesis of burn shock was emphasized as far back as 1930-1931 by Underhill and Blalock. Subsequently, this problem was given considerable attention by a great many investigators (Harkins, 1942; Artz, Reiss, 1958; Sevitt, 1957; Allgoewer, 1957; I. R. Petrov, 1950 et al.). According to the data of Underhill, Fisk and Kapsinov (1930), in the case of extensive burns, a large amount of transudate can accumulate in the area of the injury (up to 70 or 80% of the total plasma volume). Ye. D. Chervina and V. P. Trukhov (1958) point out that the level of plasma loss is a function of the severity of the burn. In various cases, with variation of the burn area from 20 to 80%, the loss of circulating plasma was 30 to 44%.

The retention of water in the tissues promotes increased permeability in the capillaries in the traumatized area, so that there is a flow of blood proteins into the intercellular fluid with subsequent decrease of the colloid--osmotic plasma pressure and an increase in the latter in the tissues. The exudation of fluid in the tissues also promotes increased hydrostatic pressure in the capillaries. Fogelman and Wilson (1954), using radioactive tracers, established that the capillary permeability increases up to three times in fatally burned human beings. In healthy individuals 1.05% of the total water in the organism passes through the capillary walls each minute; this is equal to 8.8% of the extracellular fluid. In burn victims, on the other hand, these parameters reach 4.54 and 29.7% per minute, respectively. Sevitt (1958) distinguishes between two phases in the disturbance of permeability: the first phase develops 1-2 minutes after the injury as a result of the direct thermal action on the vessels, and the second takes place after 1-2 hours. V. V. Bakanskaya (1955), using human albumin labelled with radioiodine, showed that its appearance in lymph flowing in the chests of burned dogs (24 hours after the burn) occurs in 4 minutes, while in normal animals it takes place only after 11 minutes. An increase in capillary permeability in all burn victims was observed by K. F. Dogayeva (1949-1956), L. M. Klyachkin (1960) and others. It is observed immediately following the burn and continues to increase thereafter. /185

The role of the significance of local and general disturbances to capillary permeability in the development of plasma loss in burns is subject to dispute. Many authors have observed only local changes in the permeability of the capillaries, to be precise, in the area of the thermal injury (Cope, Moore, 1944; Fine, Seligmann, 1944, and others). However, according to the data from other authors, the increase in permeability in severe burns is of a generalized nature (Netsky, Leiter, 1943, and others). In particular, the increase in capillary permeability following a burn takes place not only in the area of the injury but also in the intact internal organs (K. F. Dogayeva, 1956), while the serum of burned dogs, given intravenously to healthy animals, causes a significant increase in general permeability (V. V. Bakanskaya, 1960). Without denying the possibility of generalized disruption of capillary permeability in burns, in the opinion of the majority of authors it is still necessary to point out that the principal role in the genesis of burn plasma loss must be assigned to local disturbances.

As a result of a decrease in circulating plasma volume, a regular symptom of burn shock arises -- hemoconcentration; however, the degree of the latter

does not correspond to the level of plasma loss and cannot serve as an indicator of the severity of the burn shock. This lack of correspondence is explained by the fact that in addition to the loss of plasma from the circulation in burns, there is an unavoidable reduction of the volume of circulating erythrocytes as a result of hemolysis (B. N. Postnikov, 1944, 1952; Ye. D. Chirvina, Ye. P. Trukhov, 1958; Sevitt, 1957, and others). According to the data of Topley and Jackson (1961), in burns in human beings over 20% of the surface of the body, 15% of the erythrocytes are destroyed. An indirect indicator of hemolysis is microcytosis and fragmentation of erythrocytes, as well as the phenomenon of a deviation between the curves of the increase in hemoglobin and the number of erythrocytes (I. D. Zhitnyuk, 1953). An important symptom of burn hemolysis is bilirubinemia and urobilinuria as well as hemoglobinuria, which frequently are observed in patients in the initial stage of burn disease (L. M. Klyachkin, V. M. Pinchuk, 1969).

The principal cause of burn hemolysis is overheating of the blood in the area of the injury (to 45-65°), and the scale and rate of disturbance of erythrocytes depend upon exposure to thermal injury and the mass of heated tissue. However, it must be emphasized that tissue hyperthermia is not the only cause of erythrodiuresis in burn victims. Z. G. Pozdnyakova (1966), using Cr^{51}, established that 25-32% of the labelled autological erythrocytes administered to dogs during the first hours following a burn are destroyed, while in the case of the control animals only 5% of the erythrocytes are destroyed. At later stages (24-48 hours after the burn) the increased breakdown of erythrocytes continues. The author demonstrated that the serum of the animals, after only 2 hours have elapsed following the burn, takes on sharply pronounced hemolytic properties.

Thus, burn oligemia can be viewed as a manifestation of profound and diverse functional changes arising in the organism following burns.

The pathogenetic significance of the decrease in the volume of circulating blood is unquestionably great and many authors, particularly those abroad, assign critical significance to it in the mechanism of the development of burn shock. In recent years, data have come to light which contradict this viewpoint. As demonstrated by N. A. Fedorov and V. B. Troitskiy (1965), dogs with lethal flame burns show only a brief reduction of circulating blood volume, which does not reach a degree which would explain the severity of the pathology of the initial period of burn disease. In this context, the restoration of the volume of circulating blood frequently coincides with a deterioration of the condition of the animal. /186

Cardiac insufficiency. Considerable significance in the pathogenesis of the initial period of burn disease is assigned to the primary insufficiency of the cardiac muscle. I. B. Gurevich, S. V. Skurkovich and M. N. Khokhlova (1959) carried out extensive x-ray-kymographic and pathohistological studies on burned dogs during the period of shock. In analyzing these data, a phasal nature of the functional changes in the heart became evident. During the initial period, 10-30 minutes following a flame burn, the diameter of the heart increases during diastole, there is a marked decrease in the amplitude of the ventricular peaks, and there is also a decrease in the contraction coefficient.

The pulse and respiration increase. During the second phase (1-2 hours following the burn) all of these parameters return to normal. During the subsequent period (after 3-4 hours) there is a second wave of changes which resemble the first phase. These changes are most pronounced in the terminal phase.

Dogs which have died or been killed have been subjected to pathohistological examination. In the heart, significant filling with blood was observed 2-3 hours following the burn, large and punctate hemorrhages appeared in the connective tissue interlayers between the muscle fibers, as well as numerous small areas of fatty dystrophy of the muscle fibers with fragmentation of the latter. When the animals died at the end of the first day following the burn, some areas were seen to contain a great many fibers with basophilic homogenized protoplasm and pyknotic nuclei. These changes indicate destruction of the muscle-fiber protoplasm and a disruption of the fat-protein complex.

Pathological changes in the myocardium in human beings who died from burns were also found in earlier studies (Simonart, 1938; Zink, 1940; Allgoewer, Siegrists, 1957).

It is interesting to study the excitability and permeability of the myocardium in dogs during the period of burn shock, using the method of phase stimulation. It was shown in particular that there is an increase in the duration of the absolute refractoriness in the left ventricle and a shortening in the right, while the diastolic threshold decreased on the right ventricle and increased on the left. This indicates a dissociation of the functional state of the ventricles of the heart, i.e., it is possible to conclude that there is inhibition of the function of the left ventricle and hyperfunction of the right.

In both human beings and animals, many investigators have noticed a decrease in the minute volume of the heart during the period of burn shock. According to the data of Richards (1943-1944), the minute volume decreased to 2.9 liters, i.e., by a factor of almost 2. Similar changes were observed by Hardy (1955) in 9 recently burned patients and in experiments on dogs (Dobson, Warner, 1955, 1957; Fossard, 1962).

What is the mechanism of the decrease in the minute volume of the heart following thermal trauma? Sevitt (1957) proposed that the reason for the reduction in minute volume is oligemia and a decrease in the venous return of the blood to the right heart. However, this conclusion is contradicted by a number of experimental data. Gilmor and Handford (1956) observed that a decrease in the minute volume of the heart takes place in dogs 15 to 60 minutes following a burn, i.e., prior to the pronounced decrease in the volume of circulating blood. According to the data of other authors, the decrease in the /187
minute volume of the heart takes place during the first few minutes following the occurrence of burn trauma (Dobson, Warner, 1957; Rossard, 1962). According to our observations (N. A. Fedorov and V. B. Troitskiy, 1965), during the first few minutes following serious flame burns (20-30% of the body surface, exposure for 3 minutes) dogs show a decrease in minute volume by 48%, maintaining this low level throughout subsequent periods of observation. This decrease in the minute volume is independent of variations in the circulating blood volume (Figure 46).

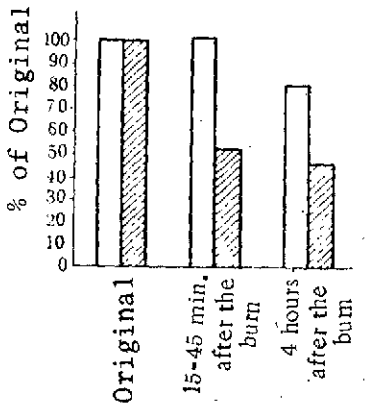

Figure 46. Change in Circulating Blood Volume and Minute Volume of the Heart Using the Fick Method in Dogs with Flame Burns (20-30% of the surface of the body, 2-3 minutes exposure). Average data from 9 experiments.

Early disruption of the contractile functions of the heart in burn victims are also supported by electrocardiography. Kayashima (1943), studying 12 burned sailors with burn areas which did not exceed 20% of the surface of the body, observed a decrease in the amplitude of all of the peaks of the ECG, particularly the T wave, while the ventricular complex assumed a monophasal appearance. Similar data were obtained by the author in experiments on rabbits. A. R. Gvamichava (1953), notes low ECG peaks in the majority of burn victims, particularly the T-wave. The author views this phenomenon as an indicator of diffuse damage to the myocardium. N. D. Voytsekhovich (1957), on the basis of an examination of 80 patients with second and third degree burns (burns covering 5-70% of the surface of the body) concludes that myocardiodystrophy developed. In the burn shock stage, the ECG's of the patients show sinusoidal tachycardia, displacement of the electrical axis of the heart to the right, and disturbance of intracardiac conductivity (blurring of the T wave). The author mentions a possible overload on the right heart; many patients showed changes in the T wave, indicating damage to the ventricles. I. B. Gurevich, R. I. Murazyan and V. B. Troitskiy (1963) also observed a voltage decrease in all peaks in patients with displacement of the S-T interval and lengthening of the P-Q interval.

Summing up the results of the investigation of cardiac function during the initial period of burn disease, we must stress the following changes:

1) an increase in the residual systolic volume of blood as a consequence of incomplete systole; this is indicated by the data from the x-ray-kymogram (a decrease in the difference between the systolic and diastolic diameter of the heart); these changes are most characteristic of the left ventricle;

2) systolic pressure in the left ventricle gradually decreases following the burn, sometimes even with unchanged arterial pressure;

3) the minute volume of the heart decreases sharply, regardless of the volume of circulating blood;

4) there is a development of tachycardia, change in excitability and conductivity, as well as phenomena of alternation of the contractions.

The combination of all of these data recorded during burn shock can be interpreted as an expression of metabolic insufficiency of the myocardium.

These results of experimental studies indicate that hemodynamic disturbances in burn shock are determined not only by a vascular decrease but also a primary decrease in the contractile function of the myocardium. /188

The most convincing indicator of the insufficiency of blood circulation during the period of burn shock is the considerable decrease in the volume and linear blood flow (Figure 47) as well as a slowing down of oxygen transport by the blood, which unavoidably leads to the development of oxygen starvation. It is primarily in conjunction with this that the majority of authors have pointed out the decrease in oxygen consumption by the organism in severe burns (L. L. Schick et al., 1965). According to the observations of S. A. Lazarevskiy et al., dogs with severe burns show a decrease of 16-20% in the total oxygen consumption. The oxygen capacity of the blood following a burn obviously increases in conjunction with hemoconcentration; the degree of oxygen saturation of the arterial blood remains high and is not abnormal. At the same time, the oxygen saturation of the mixed venous blood decreases significantly (61-49% of the original levels). The blood CO_2 decreases regularly, more in the arterial blood than in the venous blood. The arterio-venous oxygen differential increases up to 170% one hour after the burn, and up to 200% after four hours. Increasing venous hypoxemia indicates reduced blood flow, compensated by increased tissular utilization of blood oxygen. Hence, these changes clearly indicate development of circulatory hypoxia. The blood shows an increased content of non-oxidized products of intermediate metabolism immediately after a burn; for example, the organic acid level in the blood increases by more than 300% in dogs. The urine shows an increase in the non-oxidation coefficient (G. V. Derviz and V. N. Smidovich, 1958). However, the mechanism of burn hypoxia cannot be explained by circulatory disturbances alone. Some authors raise the question of the significance of tissue hypoxia during burns (G. V. Derviz, V. N. Smidovich, 1958). Tissue hypoxia during burns is explained by a change in the function of the enzymatic systems of tissue respiration.

A. P. Dovganskiy (1965) observed a decrease in the activity of succinodehydrase and cytochrome oxidase, i.e., enzymes which participate in tissue respiration processes. Z. P. Fedorova (1960) established a similar decrease in the activity of cytochrome oxidase in the mitochondria of the rat kidney during burn shock.

Obviously it must be recognized that oxygen starvation during burns has a mixed nature: hemodynamic, tissular and (in the case of injury to the respiratory pathways) respiratory as well.

Renal insufficiency. The cardinal symptom of the initial period of burn disease is disruption of kidney function. Severe burns are always accompanied by the development of acute renal insufficiency. /189

As demonstrated by the experimental studies of I. I. Zaretskiy and S. V. Skurkovich (1957), P. M. Fedonyuk (1965) and R. V. Nedoshivina (1967) on dogs in the stage of burn shock, a decrease in the excretion and concentration ability of the kidneys was found to be characteristic. As a rule, the inert and monotonic type of diuresis and phenomena of hypostenuria were observed.

The urine showed a rather considerable amount of protein and many erythrocytes and leucocytes as well as cylinders.

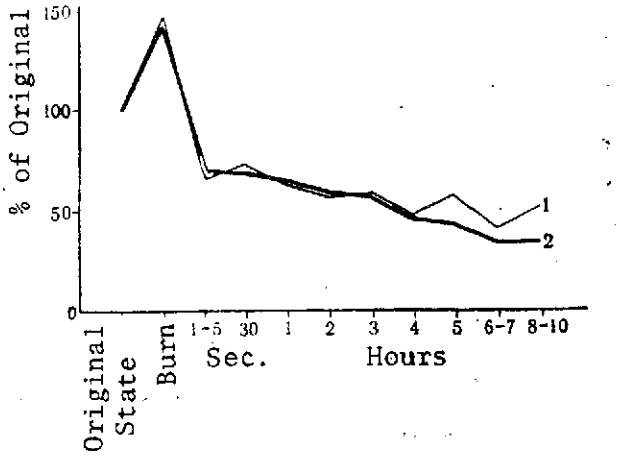

Figure 47. Change in the Rate of Blood Flow (Volume) in the Femoral Artery Using the Method of Tsibul'skiy and Klisetskiy. Average data from 14 experiments on dogs with flame burns. The surface of the burn was 20-30%; the exposure was 3 minutes.
1, Linear rate; 2, Volume rate.

One reason for the disruption of renal activity during burns is a decrease in the mass and velocity of the circulating blood as well as its thickening. However, in addition to extrarenal factors, severe injury to renal mechanisms is also significant. It may be stated that disruption of kidney function in the shock stage is caused primarily by acute disturbance of renal blood circulation. A study of the effect of renal blood flow showed a sharp disturbance of renal hemodynamia. In all burned animals, even on the first day after the trauma, the renal blood flow level decreased 2-3 times with respect to the original level.

As a rule, during the first hours following a burn there was a pronounced decrease in the glomerular filtration process (up to 54% in comparison with the original level), accompanied by increased tubular reabsorption. In other words, burn oliguria was caused by the disturbance of the filtration-reabsorption function of the kidneys. In contrast to decreased glomerular filtration, on the other hand, when the blood passed through the tubules the filtered part of the plasma increased. The plasma filtration fraction was more than 25% above normal.

The increase in the plasma filtration fraction, combined with the drop in renal blood flow, indicates that disruption of blood circulation in the kidneys is caused by spasms of the efferent arterioles of the glomeruli, resulting in decreased blood supply to the tubular sections of the functioning nephrons. The glomeruli were in a state of stagnant hyperemia, causing development of hypoxia with subsequent increased permeability of the glomerular membrane. The latter factor was responsible for the appearance of protein, erythrocytes and hemoglobin in the provisory urine.

In experiments performed under conditions of saturation of the tubular epithelium with diodrast, administered directly to study secretory activity in the kidneys, one could clearly see a drop in maximum secretion. In some experiments, the index of maximum secretion was 50% below normal. Obviously, the decrease in maximum secretion was caused by the disruption of the blood supply to the tubules, but this was not the only reason.

The development of acute renal insufficiency is directly proportional to the severity of the burn. Oliguria in the clinic and in experimental conditions is considered the prime symptom of burn shock. In this connection, it became necessary in experiments involving burns to record diuresis under dynamic conditions, as was done for arterial pressure and respiration.

Renal insufficiency in burns is accompanied by accumulation of residual nitrogen in the blood (hyperazotemia).

As we have already pointed out, the mechanism of the development of renal pathology is very complex and insufficiently explained. Considerable importance is attached to the constriction of the renal vessels. Spasms of the renal vessels in the dog and cat immediately after a burn were detected by means of renal plethysmography (P. M. Fedonyuk, 1963) and resistography of the renal artery. It may be assumed that increased reabsorption of water and sodium chloride arises under the influence of the antidiuretic hormone, aldosterone and catecholamines, whose secretion increases under the influence of thermal injury. One cause of renal insufficiency may be autointoxication, which unavoidably develops in severe burns. R. V. Nedoshivina (1967) observed parallelism between the toxic properties of blood serum and the degree of functional disturbances to the kidneys in burned dogs, and various methods of detoxification in burned animals and human beings prevent the development of oliguria. /190

Hepatic insufficiency. Following severe burns, pronounced structural and functional changes occur in the liver. V. Avdakov (1876) in his time observed degenerative changes in the liver in burned dogs. At the present time, we have highly convincing proof of the development of pathomorphological changes in the liver with varying degrees of severity during the acute period, even necroses (Wilson, 1937; Zink, 1940; Allgoewer, 1957; Sevitt, 1957; V. M. Pinchuk, 1960; Benaim, 1962, and others). Modern literature holds the opinion that necrosis of the hepatic parenchyma serves as a characteristic visceral symptom of acute burn trauma.

According to experimental studies conducted by R. V. Nedoshivina (1955), dogs develop pronounced functional injury to the liver on the very first day following a burn; this injury takes the form of disturbance of protein-formative, prothrombin-formative and excretory functions. There is a marked increase in the thymol turbidity reaction. Four hours following a burn, thymol turbidity is 1.0, with an original value of 0.4. The prothrombin time in these intervals regularly decreases up to 75%. A study of the excretory function of the liver by means of bromsulfolein tests showed increased dye retention in the blood (up to 14%, with an original value of 4.6%). Disruption of the excretory function of the liver is more severe in comparison with other functions. According to our observations, the protein and prothrombin-formative function of the liver in burns of moderate severity returns to normal in 4-5 days following the burn, while the excretory function returns only on the 30-35th day.

The majority of clinicians note pronounced and constant disruption of the antitoxic function of the liver in burn victims (B. N. Postnikov, 1952, 1957; N. A. Belov, 1957). According to the data of P. I. Shilov and P. V. Pilyushkin

(1962), a decrease in the antitoxic function of the liver (the Quick method) is already evident during the early stages following a burn, and lasts for 3 to 4 days. Under these conditions, the organism loses its resistance to exogenic and endogenic toxins, which gradually flood the organism of the burned individual. In his experiments Zweifash (1958) eliminated hepatic hypoxia by arterialization of blood flowing toward the liver or by additional perfusion. He succeeded in preventing the development of lethal burn shock. Many researchers have observed hypoprothrombinemia in burn victims (B. N. Postnikov, 1952; Allgoewer, 1957; V. I. Semenov, 1958, and others).

The principal cause of damage to the liver in burns appears to be a decrease in blood flow and the deep hypoxia which follows. Dobson and Warner (1957) showed a sharp decrease in hepatic circulation during the first few minutes following the occurrence of a burn. Similar data were obtained by V. G. Trubachev in studying erythrocytes labelled with radioactive iron. It is suggested that another reason for liver damage in burns is the action of toxic substances. Bernhard-Kreis (1939) intravenously injected a water-salt extract /191
of burned skin into guinea pigs and rabbits and observed pathohistological changes in the liver similar to those which occur during burns. An extract of healthy skin failed to produce these changes. In the experiments of R. V. Nedoshivina (1967) it was established that detoxification of a burned dog, achieved by a transfusion of blood from an animal that had recovered from burns, causes a more rapid normalization of liver function in contrast to other types of hemotherapy (Figure 48). This might possibly be explained by the antitoxic properties of the blood of animals that have recovered from burns.

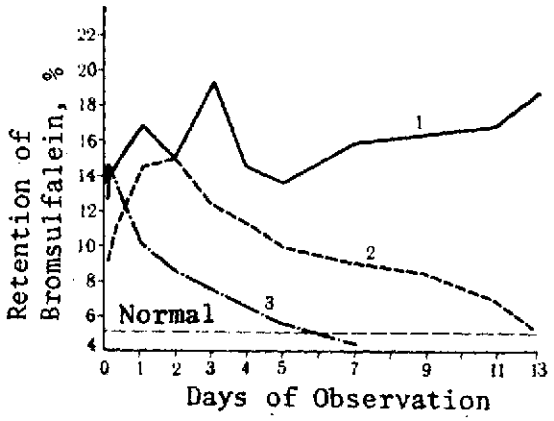

Figure 48. Excretory Function of the Liver (Bromsulfalein Test) in Dogs Following Flame Burns Without Treatment and Against a Background of Immunohemotherapy (R. V. Nedoshivina). 1, Without treatment; 2, Administration of normal serum; 3, Administration of immune serum.

Protein metabolism. One of the most important phenomena of burn disease is the disruption of protein metabolism. It occurs during the initial period of the burn and reaches its maximum in the stage of toxemia, setting the stage for subsequent development of burn exhaustion. For patients with burns of moderate severity, increased protein losses last up to 30 days; during the first 10-15 days the patients lose 1-1.5 kg in weight daily (Ye. V. Gubler, 1965). Characteristic symptoms of the pathology of protein metabolism in burn victims are hypoproteinemia and a change in the fractional composition of serum proteins.

Hypoproteinemia develops during burn shock and its degree

depends upon the severity of the burn (Yu. M. Gefter, G. F. Milyushkevich, 1949). It should be pointed out that hypoproteinemia may not develop during the first two days after a burn, this apparently is related to hemoconcentration. Burns are typically characterized by a drop in the plasma albumin fraction and an increase in the α_1- and α_2-globulin fractions (Allgoewer, Siegrist, 1957; P. M. Pilyushkin, 1962). Protein deficiency develops in burn victims as a result of loss of proteins from the surface of the burn, as a result of a loss of proteins from the vascular bed into the spaces between the tissues, through excretion with the urine, and finally as the result of generalized breakdown of tissue proteins. The protein losses amounted to 1.5 to 5 grams per 1% of burned surface, while the total loss may reach 94 grams of protein daily (D. Ye. Laynturg, L. F. Klimenko, 1968). According to the data of other authors, these values may reach still higher levels -- up to 8 grams for each 1% of burned surface. According to the studies of Lynch et al., (1964), the burned area may retain more than 44% of the radioiodine--labelled albumin that was administered via the blood, while only 5% is retained in healthy persons.

Generalized breakdown of proteins is the most important cause of protein deficit in the organism of a burn victim. The increased catabolism of proteins in a burn victim indicates a negative nitrogen balance, increased excretion of creatine, ammonia, peptides and amino acids with the urine, while residual nitrogen accumulates in the blood. It is interesting to examine the question of the location of increased proteolysis. D. Ya. Ryvkina (1945) suggested the /192 hypothesis of a generalized splitting of proteins in the organism after a burn. This view was based on data on the dynamics of the ratios between non-protein nitrogen and total nitrogen in various intact tissues (liver, skeletal muscle) as well as damaged skin. Increased protein breakdown in burn victims is caused by activation of proteolytic enzymes in all tissues.

Beloff and Peters (1945) separated a proteolytic enzyme from burned skin which lyzed casein, globulin, albumin and skin proteins. Ungar and Damgaard (1955) observed increased activity of proteolytic enzymes in skin sections from a guinea pig following heating in vitro. Goldfraind (1957) found a proteolytic enzyme in the fluid from a burn blister on a frog. T. L. Zayets et al. (1963, 1965), and T. A. Borisova (1965) found an increase in the breakdown of proteins in undamaged tissues (muscle, kidney, liver) in a burned rabbit, which corresponded in all respects to the increase in the activity of the proteolytic enzymes (catepsins). It is interesting to note that burns are accompanied by increased activity of proteases, not only in the cytoplasm but in the nuclei as well.

Generalized protein breakdown leads to accumulation of toxically active substances, some of which possess a high degree of physiological activity (histamine, bradykinin). Their significance in the pathogenesis of the initial period of burn disease is undisputed. This view is illustrated clearly in interesting works by other authors, who succeeded in increasing the survival time of animals and prevented the development of the individual symptoms of burn disease by preliminary administration of inhibitors of proteolytic enzymes. Thus, Koslofski and Paschkeit (1960) administered trasilol to burned rats; this

is a preparation which inhibits proteolytic enzymes, thereby preventing the development of oliguria, increasing the survival rate of the animals, and decreasing the excretion of amino acids with the urine.

Water exchange. Disruption of water exchange is a normal and typical phenomenon associated with the initial period of burn disease. The pathology of water exchange in burn victims usually is evaluated on the basis of indicators of water balance, plasma loss, edema and oligonuria. Extreme thirst is one of the constant symptoms of burn shock. In serious burns there is movement of a considerable amount of fluid, primarily into the region of the burn, where up to 70-80% of all the plasma may be concentrated (Underhill, 1930). Edema is most pronounced in burn victims 48 to 72 hours after the burn; it is promoted by massive infusion therapy.

In recent years, our knowledge concerning the state of water exchange in burn victims has been considerably increased by the use of new methods of investigation which make it possible to measure extracellular fluid (ECF) and extravascular extracellular fluid (EEF). In burn victims there is a significant (up to 50%) increase in EEF. The dilation of the extracellular fluid space is a function of the accumulation of water in tissue spaces.

Somewhat later, Stirman, Prudden and Jaung (1955) also observed an increase in extracellular fluid in patients with third degree burns over 30-80% of the body surface.

In contrast to these studies, Fogelman and Wilson (1954) and Harrison and Becker (1957), working with seriously burned dogs which had not been given treatment by infusion therapy, noticed a decrease in the EEF during the very first hours following the trauma. Determination of the total water by means of heavy water did not reveal any important deviations from the original standard, /193 which gave the authors a basis for assuming the possibility of a movement of water into the cells (cellular hydration). N. A. Gorbunova and V. B. Troitskiy (1964), in experiments on dogs after burns, observed regular changes in the ECF which depended upon the severity of the injury. In cases where the dogs died during the first few hours following the burn, the ECF and EEF decreased noticeably; this was considered by the authors as an indication of a transfer of water from the tissue spaces into the cells. The pathogenetic significance of cellular hyperhydration in serious burns can scarcely be over-estimated, since excess water accumulation in the cells unavoidably leads to profound disturbances of their biochemical processes.

The consequences of extreme hyperhydration of the cells is clearly evident in the experiments of N. I. Kochetygov (1962, 1964) who injected rabbits with 150 ml/kg of pure water for 7-8 hours following a burn. Disturbance of water homeostasis of the cells in these instances resulted in serious consequences, taking the form of hyperazotemia, hyperkalemia and development of spasms. The majority of the experimental rabbits died during the first three days after the burn, in contrast to control rabbits with the same burns, which did not receive water or received physiological solution.

Any change in water metabolism is unavoidably linked to a disruption of electrolyte balance. The sodium content increases in thermally injured tissues, while potassium concentration decreases. Opposite changes occur in the blood. Potassium exudation from burned tissues is particularly marked in burns involving considerable hyperthermia of skeletal muscles.

Immunological reactivity. In burn shock, there is a sharp inhibition of humoral and cellular factors of nonspecific resistance of the organism.

Fumarola and Fransevea (1958) showed that the level of properdine in the blood of burned rabbits decreases sharply and progressively after a burn. While the properdine content in a normal rabbit is 63 units/ml, the amount of this substance drops to 23 units/ml only 4-8 hours following burn trauma and to 5 units/ml in 56 hours. These data were confirmed in patients with serious burns (R. I. Muradzyan and I. L. Chertkov, 1960).

Burned patients show a decrease in the complementary activity of the serum during the first few days following thermal injury (I. N. Ishchenko, M. N. Lebedeva, 1937; V. D. Bratus', 1967 and others). The phagocytic activity of the leucocytes is consistantly suppressed. Lieddberg (1961) studied the phagocytic activity of the cells of the peritoneal exudates of healthy and burned guinea pigs following administration of Bacillus pyocyaneus into the abdominal cavity. While the healthy animals contained, in addition to polymorphonuclear cells, approximately 67-70% which were capable of phagocytization, this figure /194 is only 46% in burned animals. Inhibition of phagocytic reactions was also observed in patients following burns. P. S. Krasnopevtsev and A. A. Menkina (1967) found a sharp decrease in phagocytic activity of leucocytes during the first few hours following a burn, while in patients with deep and extensive burns the phagocytic capacity of the leucocytes was blocked for up to 5-7 days after the trauma. A. A. Aslanyan (1966) observed a lowered phagocyte count only 6 hours following thermal trauma in patients with burns of variable seriousness and extent. In the opinion of many investigators, the status of phagocytic activity of leucocytes can serve as a sensitive indicator of the nonspecific immunological resistance of the organism following a burn.

The studies of N. A. Fedorov and R. V. Nedoshivina (1970) confirmed a sharp suppression of the absorptive function of the reticuloendothelial system in dogs after burns (Figure 49). This takes the form of a prolongation of the time required to cleanse the blood of colloidal radioactive gold (Au^{198}) previously injected into the vascular bed. Thus, the cleansing of the blood to remove Au^{198} in burn victims is completed in 35-40 minutes as compared to a normal 13-15 minutes. In burns of moderate severity, the absorptive function of the reticuloendothelial system was restored only by the 21st to 23rd day.

Suppression of humoral and cellular factors of nonspecific resistance permits development of local and generalized infection, frequently complicating the course of burn-induced disease.

Thus, the initial period of burn disease is characterized by various far-reaching and distinctive functional disturbances, in no way resembling the

changes observed in shocks of different etiology. One can agree with T. Ya. Ar'yev who says that the first period of burn disease is conditionally referred to as burn shock probably more because of tradition than for any other reason.

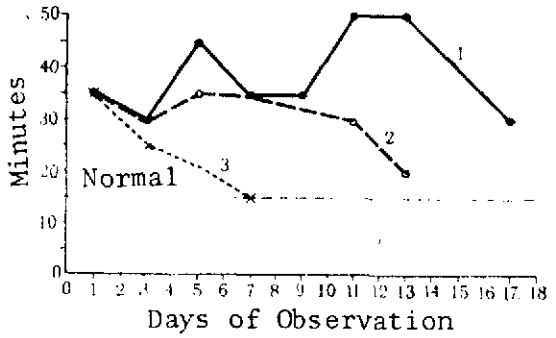

Figure 49. Absorptive Function of Reticuloendothelial System (Method with Colloidal Radioactive Gold Au^{198}) in Dogs with Flame Burns (Surface of the burn 20-30%, exposure 2 minutes) Without Treatment and Against a Background of Immunohemotherapy (R. V. Nedoshivina).
1, Without treatment; 2, Administration of normal serum; 3, Administration of immune serum.

Theory of Burn Shock

The neurogenic theory. Over the last 20-30 years the neurogenic theory of burn shock has come to light and been accorded wide recognition. The studies of Soviet pathophysiologists (I. R. Petrov, A. N. Gordiyenko, G. L. Frenkel') and surgeons (A. V. Vishnevskiy, A. A. Vishnevskiy, M. I. Shrayber and others) have become very famous; these individuals have played leading roles in the development of the neurogenic theory of shock. A. V. Vishnevskiy characterized burn shock as a complicated neurodystrophic process that follows overstimulation of the nervous system.

At the present time, many facts have been accumulated which characterize the activity of various segments of the nervous system and its influence on other systems during burn shock. The phase sequence of development of excessive inhibition in the cerebral cortex and subcortical centers has been established (I. R. Petrov, 1950). One of the characteristic features of burn disease was found to be the relatively late onset of exhaustion of the vasomotor center. Thus, V. B. Lemus (1965) found that the magnitude of the pressor vascular function in rabbits in response to ammonia aspiration increases sharply 2 hours after a burn and does not decrease thereafter for 4 hours. These data explain to us the prolonged retention of arterial pressure within normal limits following serious thermal trauma.

We know that burns injure a portion of the hypothalamus. L. I. Muzykant (1965) performed a histological and histochemical study of the anterior hypothalamus, hypophysis and adrenal cortex of burn victims who had died as a result of their injuries. It was found that the reaction of the neurosecretory system following a burn takes the form of an accumulation of a large quantity of neurosecretion in the neurons of the supraoptical and paraventricular nuclei of the hypothalamus and in the pituicytharic fibers of the posterior hypophesis. /195

Many clinicians have shown the significance of disruption of the diencephalic region and the reticular formation in the development of various symptoms of burn disease (Lamy, 1959; Ye. D. Bulochkin, 1965). Considerable importance also attaches to the disturbances of the endocrine system. Many researchers feel that the stress pattern regularly develops in burns. Thus, the activation of the adrenal cortex and an increase in its glucocorticoid function was demonstrated as the result of the direct influences of the hypothalamus (Sevitt, 1954; Birke et al., 1958; Rennels, Timmer, 1962), beginning only 30 minutes after the burn (V. B. Lemus, 1965). Another point which is of interest is the experimental research of Knigge et al. (1959) who studied the functional status of the hypothalamus-hypophesis-adrenal system in angiostomized dogs on the basis of the indications of the amount of corticostrone in the blood, coming from the adrenals. It was shown that this system normally reacts to thermal trauma in two phases. An initial brief rise in the secretion of glucocorticoids is followed by a decrease, but this is followed by another activation of secretion. T. L. Zayets (1969) demonstrated an increase in the amount of 11-hydroxycorticoids in the blood of rats by 154% only 30 minutes following a burn. However, on the next day their content was found to be below the original level. Hence, hypersecretion of corticosteroids following a burn is characteristic only of the period of the stressor reaction, i.e., at the very beginning of burn shock. Later, glucocorticoid insufficiency sets in. At the same time, the secretion of catecholamines by the adrenal cortex increases during the entire initial period of burn disease. It may be concluded that certain symptoms of burn shock are caused by stressor changes in the organism of the burn victims. For example, an increase in the proteolytic activity following a burn may involve hypersecretion by the adrenals, since it is prevented by adrenalectomy. In burn rabbits, against a background of disruption of the supraoptical nuclei of the hypothalamus, there is a decrease in autolysis in intact muscle (T. Ya. Zayets, 1969). The generalized spasm of the arteriolar system is due to the secretion of adrenal catecholamines.

The neurogenic concept of pathogenesis of burn shock in its general form is not novel, although many of its concrete aspects are not supported by factual data and are therefore subject to dispute. According to this theory, the symptoms of burn disease in the acute period involve disruption of the regulatory and trophic activity of the nervous system under the influence of excessive painful stimulation. This view raises questions inasmuch as in serious burns involving shock the nerve endings in the skin die rapidly under the influence of high temperature and the pain factor can have a pathogenetic effect only during the first minutes after the burn, especially since patients with deep burns rarely complain of severe pains (T. Ya. Ar'yev, 1966).

Proponents of the neurogenic theory state the view that exhaustion of nerve centers develops under the influence of powerful nervous impulsation from the focus of injury soon after the trauma. This view is also subject to dispute. It has been shown by biochemical studies that in burn trauma there are no significant changes in the central nervous system for a long period of time. Thus, V. B. Lemus (1965) demonstrated that the ATP level in the brain tissues /196
of seriously burned rats usually rises within 1.5 hours following the burn and remains high for 6 hours. The creatine phosphate level does not change during the first 1.5 hours and decreases only 6 hours following the injury.

Polarographic studies have shown that serious burns in dogs are followed by the oxygen tension in the brain tissues remaining at rather high levels for a long period of time and dropping sharply only in the terminal period (Ye. A. Kovalenko, V. B. Troitskiy, 1966; L. L. Shik, A. N. Kuznetsova, B. I. Lektorskiy, 1965). This fact indicates that the blood supply to the brain in burn shock remains at a level sufficient to satisfy the oxygen needs of the brain.

Toxic theory. Among the teachings regarding the pathogenesis of burn disease, one of the first was the toxic theory which explains the origin of various functional disturbances as poisoning by products of tissue origin. This theory is supported by considerable experimental data which demonstrate the toxicity of blood, skin extracts, fluid from blisters of burned human beings and animals.

V. S. Avdakov (1876) was the first author to describe the toxicity of blood from burned animals. The pathogenetic significance of the toxemic factor in burns was demonstrated convincingly by M. Geyde and V. Vogt (1913) who were the first to use the method of parabiosis on rats for this purpose. It was shown that when one parabiont was burned, its intact partner showed clinical symptoms of burn disease. After 24 hours both parabionts died with the same symptoms of serious intoxication. Similar data were obtained by R. A. Vakoretsts (1922) in experiments on dogs with vascular parabiosis. Studies in this direction are being conducted at the present time by N. A. Fedorov and V. S. Barkaya (1964). In experiments on rats of the "August" strain, the pathohistological changes in parabionts were studied following application of thermal trauma to one of them. It was shown that changes develop in the intact partners which are characteristic of thermal burns. Thus, their livers showed a dilation of the intracellular space, the cell outline became unclear, and foci of necrosis were constantly cropping up. The kidneys of intact parabionts, like those of burned animals, developed numerous hemorrhages, especially in the cortical layer. Large groups of tubules were in a state of dystrophy.

Considerable interest attaches to the studies of Pfeiffer (1963) who found that the urine in the serum of burned animals has toxic properties. The toxic substances in burns are products of the breakdown of the proteins themselves -- diamino acids and various proteinogenic amines. Recently, many researchers have confirmed the basic views of the studies of Pfeiffer concerning the toxicity of blood in urine following burns (N. I. Ishchenko, M. P. Pavlova, 1937; B. V. Lemus, 1949; Monsaingeon, 1949).

To test the burn toxins, we worked out a method of hemoculture which consists in the in vitro cultivation of pieces of human leucocyte membrane on a certain nutrient medium (N. A. Fedorov and I. K. Koryakina, 1960). In the experiment, equal amounts of serum to be investigated were added to the nutrient medium, while Ringer solution was added to the controls. The material was cultured by the hanging drop method, at 37° for 18 hours. The indicator of biological activity of the investigated material was the size of the zone of migration of the leucocytes around the cultivated piece of leucocyte membrane. The studies revealed a sharply inhibitory effect on leucocyte migration, /197

produced by serum from animals and human beings after burns; a biphasal nature of the changes in the toxic properties was observed. The toxic effect was clearly pronounced after 6-24 hours, then decreased, and in some cases even vanished 48 hours after the burn. The second wave of toxicity starts 3-5 days after the burn and lasts for a long time (17-35 days). Rosenthal (1961, 1962) used a suspension of cancer cells (HeLa) in Igl medium for this purpose. The experiments showed lack of growth in the cultures following the addition of serum from burned patients.

The toxicity of serum from burn patients was demonstrated in a most convincing and lucid fashion in the case of mice with blocked reticuloendothelial systems. It is known that blockage of the reticuloendothelial system sharply increases the sensitivity of animals to burn trauma. Lowrence (1966), N. A. Fedorov and R. V. Nedoshivina (1970) showed that serum from burned dogs and human beings, collected during the period of shock and administered intraperitoneally to mice, produced nearly 100% mortality among the mice in the course of 12 hours following injection 1-1.5 hours after blockage of the reticuloendothelial system. It is interesting to note that in these experiments biphasal dynamics of the toxicity of the serum from burn victims was observed.

In addition to blood, exudates from a burn site have toxic effects. Thus, exudates obtained 48 hours following a burn, when injected into rabbits, produced a marked toxic effect and even death. The toxic component of the exudate was pseudoglobulin.

Rosenthal (1959) developed a method for obtaining diffusion products from burned skin. He injected 30 ml of air beneath the skin of the back in rabbits, i.e., he produced a clearly prominent bleb which was submerged in water at 95°. Then the pouch was washed out with Tyrode solution. The extracted fluid was dried and the dry residue obtained. The material which was obtained turned out to be toxic and lethal to mice and rats under conditions of acute and chronic experiments. The toxic factor passed through the semipermeable membrane and was characterized by thermostability and partial precipitation by 80° ethyl alcohol.

There is no doubt that extracts from burned skin also have toxic effects. In the experiments of Schuetz (1936) an extract from burned skin, when injected into another animal, caused death with development of pathological anatomical changes characteristic of serious burns. Injection of extracts from intact skin failed to produce any such changes. Lowrence (1956) showed that a water-salt extract of burned skin from mice, injected into healthy mice, causes a serious reaction which is particularly marked in animals with previously blocked reticuloendothelial systems. Kowlowski, Urbaschek and Verstey (1966) observed death of mice in 10-12 days following intraperitoneal administration of a water-salt extract obtained from burned skin. The toxicity of the skin extracts was evident only in the case of early removal of the skin following the burn and immediate administration of the extracts following their preparation. The toxicity of the extracts was a function of microbial contamination.

Hence, as indicated by numerous studies, the starting point for burn toxemia is evidently the focus of the thermal injury. Later, the toxic substances penetrate into the blood.

It is worth mentioning the studies of Simonart (1958) who showed the primary significance of the toxemic factor in thermal burns, and not plasma loss. /19 The author produced burns in frogs by submerging the hind leg up to the shin in water at a temperature of 50-60° for 15 seconds. Thermal trauma was accompanied by edema of the extremity. The animals died in several days. The application of a tourniquet above the point of the burn immediately after the trauma saved the animal and prevented edema. However, removal of the tourniquet caused death of the animal, although edema did not develop. Simonart pointed out the considerable similarity between the damage characteristic of thermal burns and the changes which occur following subcutaneous injection of solutions of peptone. In the case of rabbits, only this method of administration was found to be dangerous, and a significant amount of peptone can be administered intravenously without any serious complications. The author suggested that the substances which cause intoxication arise in the vicinity of the subcutaneous injection. The study of the edematous fluid caused the detection of protein fractions whose toxicity was clearly demonstrated in experiments on animals. At the same time it was shown that subcutaneous and intraperitoneal administration of serum albumin, denatured by heating, causes similar toxic effects.

Hence, on the basis of Simonart's hypothesis, thermal burns cause denaturing of proteins with subsequent enzyme hydrolysis, with the toxic products being absorbed into the blood. Activation of proteolytic enzymes in the edematous fluid during burns serves as the most important argument in favor of this hypothesis.

Monsaingeon (1963), continuing the studies of Simonart, proved the toxicity of purified serum albumin heated to 80°. Subcutaneous injection of the products obtained caused death of frogs with symptoms characteristic of a burn. In the author's opinion, the toxic effect is not caused by the denatured protein as such but by the products of its fermentative splitting.

The fact of autointoxication in burns is unquestionable. Nevertheless, this theory does have its weak aspects. Thus far, there has been a lack of accurate information on the chemical nature of the burn toxins and also no proof of their specificity to burn trauma. The mechanism of the action of toxic substances in burns still remains unclear and it has not been determined where they are formed. There are no precise criteria which can be used to differentiate, for example, between toxemia of histiogenic origin from septicopyemia.

In recent years the idea of noninfectious immunology of burn disease has developed (N. A. Fedorov et al., 1955, 1957, 1960), creating a new stage in the study of burn toxemia. By means of anaphylaxis and desensitization according to Zil'ber it has been possible to show convincingly the development of autoantigen in burned skin; it is not found in healthy animals and human beings. Burn antigen lacks species specificity, but it does have nosological

specificity, i.e., it is not observed in tissues subjected to different kinds of injury. Burn antigen is found in the blood for 10-15 days after a burn. Recently, by means of modern immunochemical research methods, it has been possible to confirm the existence of different antigen structures of burned and healthy skin (V. A. Mazurenko, 1968; I. I. Kolker, 1970; B. Ye. Movshev, 1970).

An important aspect of this research was the attempt to find proof of autoimmune processes in an organism without a burn. At the present time, we have numerous indications of the formation of "antiburn" antibodies in human beings and animals that have been subjected to burn trauma. The studies of N. I. Kuznetsova, S. V. Skurkovich (1959), V. N. Kazakova (1965) and others /19
have shown that serum from burned human beings and animals has the ability to confer the positive immunological reaction of complement binding with antigens from animal tissues. This ability has a certain degree of selectivity for antigens from burned tissues regardless of their species and organ membership. The serological activity of serum involves β- and γ-globulin fractions; the active beginning is thermolabile and cannot be eliminated by dialysis. The maximum titer of antibodies is observed in human beings who have recovered from serious burns. Antibodies can be found, beginning with the second month and lasting up to one year, and in certain cases they can even be found for 5 years after the burn. The data from Czech authors is interesting (L. Pávková, Ya. Doležalová, 1960); using the reaction of colloid agglutination and the Boyden method, they observed antibodies in the serum of burn victims that react specifically with antigen components from burned skin.

What is the biological significance of "antiburn" antibodies? The results of our studies of antitoxic substances in serum from burn victims who are recovering answer this question.

By means of the hemoculture method it was shown that the serum of those who have recovered after burns in 30-40 days possesses antitoxic properties with respect to toxic serum collected 24 hours after a burn. In fact, if we mix toxic serum beforehand with serum from those who have recovered from burns and keep this mixture in a thermostat for 3 hours, the toxic effect will decrease or disappear completely. In control experiments in which toxic serum was incubated together with the serum from normal animals, no detoxifying effect was observed. The burn antitoxins occur in human and animal blood on the 30th-40th days following thermal trauma and can be observed for many months, with their titer reaching 1/64 or more. It should be emphasized in particular that the burn antitoxins which are bound with β- and γ-globulins appear in the blood at the same times as the complement-binding antibodies.

This experimental material provides a basis for suggesting hypotheses which hold that burn trauma contributes to the formation of specific antigens in the skin -- toxins with subsequent autoimmunity reactions. The antibodies which form in the organism of a burn victim during recovery confer a protective effect (i.e., neutralizing effect) with respect to the toxic products that flood the organism following serious burn trauma.

All of the above served as the theoretical basis for the use for therapeutic purposes of serum from those who had recovered from burns. Those who were treated with this serum stopped vomiting, showed decreased leucocytosis and hemoconcentration, an increased volume of circulating blood, normalization of kidney and liver function in shorter spaces of time, a decrease in the intensity of protein breakdown, increased phagocytic activity of the leucocytes, prevention of the development of anemia, a speeding up of the formation of granulation of the site of thermal injury, and rapid normalization of mineral metabolism (N. A. Fedorov, S. V. Skurkovich, 1955; R. V. Nedoshivina, 1967; I. K. Koryagin, 1968; B. Ye. Movshev, 1970, et al.). Special emphasis should be placed on the fact that the serum from those who have recovered from burns possesses the ability to reduce blockage of the reticuloendothelial system in burned animals, which to a significant degree leads to an increase in the nonspecific resistance of the organism with respect to the action of infectious agents. Thus, the results of research on nonspecific immunology of burn disease, cited often in Soviet and foreign literature, reinforce and develop the /200
toxemic theory of burn disease.

In the current literature, considerable attention is devoted to the problem of the significance of the microbial factor in the mechanism of the development of burn intoxication. There is a basis for concluding that in addition to toxin of histogenic origin, endotoxin from E. coli appear in the blood during burn shock (T. V. Golosova, M. S. Murasheva, 1968). The following facts indicate this. During the first few days following thermal burns, E. coli can be cultured from dog blood; the blood of animals which have recovered shows specific antibodies with respect to the endotoxin of this bacillus, sometimes at a high titer; the serum of animals that have recovered is in some cases capable of preventing the death of mice following administration of a lethal dose of pure endotoxin.

On the basis of the above we have concluded that burn disease is accompanied by the phenomena of toxemia at all stages of its development. The toxemia associated with each period has its own peculiarities, governed by the nature and mechanism of action of the factors participating in its formation. Toxemia develops clearly during the period of shock and, it must be assumed, is formed with the participation of histiogenic and possibly bacterial factors. Therefore, the battle against toxemia must begin during the period of burn shock which, we must assume, considerably increases the percentage of recoveries from burns.

On the basis of the above we can conclude that nowadays, thanks to the concentrated studies of researchers and clinicians, definite success has been achieved in understanding the essence of the pathogenesis of the initial period of burn disease. Nevertheless, there are still many aspects of this important problem that require further study.

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OVERHEATING

Professor A. Yu. Tilis

Maintaining constancy of the temperature of the internal environment in /202
higher homiothermal vertebrates is based on the continuous operation of regulatory systems that balance heat loss to the external environment with its formation in the body. As we know, in addition to the "endogenic" heat which is formed in metabolic processes, the organism can, under certain conditions, obtain a specific amount of heat from the external environment. The "external" heating is particularly significant under the direct influence of solar radiation, as well as in the presence of intensive heat stress from heated objects (as in the case in many industrial production situations) or from the ground which has been heated by the soil, stones, and so forth (so-called "secondary" radiation). With a high temperature in the surrounding medium, convective heating is also possible.

Under optimum external conditions, the increase in heat loss in accordance with the changes in heat production in the "external" heating is ensured by complex mechanism of physical thermoregulation composed of the dilation of the vessels in the skin and increased water evaporation from the surface of the body (sweating, polypnoeic reaction in many mammals and birds).

In the case of evaporation from the surface of the skin (or the mucous membranes of the mouth, tongue and upper respiratory pathways in animals which do not have sweat glands) 1 ml of water carries 0.58 kcal of heat away from the evaporating surface (due to the latent heat of evaporation). With an air temperature of about 35° and moderate humidity, a man loses an average of about 5 liters of perspiration a day, corresponding to the loss of 2,900-3,000 kcal of heat. Under more rigorous conditions, sweating can reach 2-3 liters/hour (and heat loss accordingly rises to 1,000-1,700 kcal/hour). Equally effective /203
(although less economical from the standpoint of energy consumption by the organism) is the increase in heat loss by evaporation using the mechanism of polypnea.

The intensity of evaporation of a liquid from the surface of the body at a given external temperature is inversely proportional to the moisture in the surrounding air. At a relative humidity of 100% the heat loss by evaporation disappears almost completely. With low atmospheric humidity (20-25%) man can maintain homiothermia for a long time at 60-65°, while at an air temperature of 28-30° and 100% humidity overheating may occur even with moderate muscular exertion.

The phenomena of overheating must be considered as extreme states, inasmuch as disturbances of many functional systems (as well as organs) develop under these conditions, frequently threatening the life of man or animals.

The higher the heat production of the organism, the easier it is for the relative insufficiency of heat loss to become evident. The intensity of the external heating, difficulty in heat loss by evaporation, and increased heat

production as a result of etiological overheating factors may arise under various conditions under very different combinations. In this connection, we can vary the picture and the dynamics of development of the pathological process.

Depending on the factors (external or internal) which are of predominant significance in the given case, overheating can be categorized in terms of its origin as exogenic or endogenic, although these divisions are always conditional to a certain extent. Thus, for example, endogenic overheating, caused by stimulants of metabolism and heat production, always depends in turn upon the conditions of heat loss and does not develop at low external temperatures. With external conditions being the same, overheating is much more likely to develop during muscular work than at complete rest.

Hyperthermia during overheating is a passive phenomenon. While fever hyperthermia is linked to the active restructuring of the apparatus of thermoregulation and is independent of external temperature, in overheating retention of heat in the body develops against a background of maximum stress on the physiological mechanisms of heat loss as a result of their relative insufficiency for the given conditions. This is determined to a large extent not only by the opposite nature of the activity of the thermoregulatory apparatus during fever and overheating, but also the profound difference between all of the symptoms of these states with an equal rise in body temperature.

The rate at which the phenomena of overheating develop, as well as the course of a pathological process, depend upon the intensity and force of the physical agent as well as on the functional state of the organism of the animal or man. In a temperate climate, heat stroke and sunstroke are usually encountered in spring and summer (Hiller, 1902). While the Sun's rays have an influence on a clothed person, warm clothing constitutes still another source of heat.

An important factor which influences the development of overheating is high atmospheric humidity. As far back as 1883, S. D. Kostyurin found that dogs died much more rapidly at lower temperatures in an atmosphere saturated with water vapor, than they did in dry air. Pearson describes cases of heat stroke recorded in February 1955 in Perth (Australia), of which 14 had a lethal outcome. The reason was the unusual heat which occurred immediately after torrential rains.

Considerable importance in the development of heat stroke is attributed to the rate of movement of air. Usually hyperthermia develops in hot, still /20
weather. The important factors which promote overheating are the individual characteristics of the organism which promote changes affecting the respiratory organs, cardiovascular system, excretory apparatus and disturbances to other functional systems. The most important factor which promotes development of heat stroke is increased fat deposition (Hiller, 1902).

In the course of development of symptoms of overheating, the rate at which the organism activates its thermoregulatory mechanisms, aimed at maintaining a constant body temperature, and the nature of its functioning, are of

critical significance. Hellon and Jones (1956) showed that persons who lived under hot-climate conditions are capable of excreting more perspiration than those who live under temperate climate conditions, carrying out the same muscular work in a given time. The significance of the duration of the latent period of reaction of sweating was noted (M. Ye. Marshak, 1965): not only the magnitude is important (A. B. Lekakh, 1940) but also the efficiency of sweating, associated with the amount of perspiration evaporated per unit time (L. M. Sidorova, 1935).

The increased formation of skin pigments is also a protective measure against overheating. Pigmented skin has increased sweating capacity with respect to solar radiation and improved regulation of heat exchange (I. T. Kashkinbayev, 1934; Franz, 1937).

Age characteristics play an important role in the development of overheating. Hellon and Lind (1956) point out that in young persons (23 years old) working in a location with a high temperature, more perspiration is given off in comparison with persons 43 years older. Elderly persons are more sensitive to high temperature conditions. On the other hand, in view of the insufficient development of thermoregulatory mechanisms, overheating can occur particularly easily during the first months of life in the newborn child, aged up to 1 year (P. N. Veselkin, 1961).

Individual predisposition to overheating may be observed in animals as well. In particular, one can find heat-resistant dogs whose body temperature rarely goes above 40.5-41.5°, even if they are subjected to overheating for 4-5 hours. In other dogs that are less resistant to high ambient air temperature, body temperature rapidly reaches 42° or more during overheating (M. D. Sheynerman, 1931; A. Yu. Tilis, 1947).

Some researchers have observed that the rate of overheating of animals of a given species is a function of size and weight; at a given ambient temperature, death occurs sooner in larger animals (Ye. N. Kogan, 1935; A. D. Slonim, 1941).

The individual resistance of animals to solar-heat overheating is determined by other factors, including the length and color of the fur (A. D. Slonim, 1962; Bonsma, 1949; Dowling, 1956; Rhoad, 1938). Overheating is also promoted by factors which increase heat formation, such as hyperthyrosis, acromegaly and other disturbances of endocrine regulation.

A special role in the development of overheating is played by a shortage of water in the organism. Pitts, Jonson and Consolazio (1944) demonstrated that limited fluid intake under conditions of exposure to a high ambient temperature is accompanied by loss of working capacity and more rapid development of the symptoms of overheating.

In animals, symptoms of overheating also develop more easily under the conditions of a limited drinking regime (A. T. Astankulova, 1958).

A shortage of water in the organism under conditions of prolonged exposure /20
to a high ambient temperature is accompanied by increased protein breakdown and disturbance of mineral metabolism, i.e., it is one of the factors that predispose animals to the development of overheating (S. N. Predtechenskiy, 1901).

Types of Overheating and the General Characteristics of Their Development

In numerous experimental studies, beginning with Bernard (1871) and ending with observations on human beings in heat chambers, the general dynamics of the development of acute overheating have been studied quite fully. In the case of rapid introduction into a medium with a high air temperature or into a zone of exposure to intensive heat radiation, mobilization of regulatory mechanisms for increasing heat output is preceded by a short latent period ("indifferent"). The next period ("stimulation") is characterized by the activation of (and later maximum stress on) the reactions of increasing heat output, beginning with a gradual increase in body temperature and periodically developing motor excitation, restlessness, increased reflex excitability (in man -- increased stimulatibility; outbursts of unmotivated anger, severe headache and dizziness, racing of the heart, fatigue, sometimes nausea and vomiting). These phenomena are so serious from the subjective standpoint that in pyrotherapeutic practice the use of physical heating is usually combined with administration of analgesics and calming agents. The use of oxygen and heat production during this period gradually increases in a known ratio to the increase in body temperature (A. D. Slonim, 1952; V. D. Lindenbraten, 1967, and others), which has to do with an increase in the work of the respiratory musculature and the heart, increased motor activity, and an increase in body temperature with the influence of heat upon the metabolic reactions in the tissues. A characteristic feature of overheating in this stage is the elimination of chemical thermoregulatory reactions to cold stimuli (A. D. Slonim, 1952), while in fever this reaction appears quite clearly. The third period ("exhaustion") is characterized by adynamia (in man -- entry into stupor); slowed breathing, drop in arterial pressure and relative decrease in gas exchange (V. D. Lindenbraten, 1967) and is essentially a preagonal period. In man, the transition from the stage of excitation to the stage of heat stroke may be very rapid; in the literature, many cases of lethal outcomes from this factor have been described, involving non-acute application of physical overheating for therapeutic purposes (Gore, Isaacson, 1949; Hartman, 1937 and others). Death usually ensues with the first stoppage of breathing at a body temperature of 42.5-43.5°. The most frequent cause of death in acute overheating is profound disruption of the function of the central nervous system as the result of disruption of blood circulation, hypoxia and the damaging effects of heat and toxic products of disturbed metabolism on the nerve centers (Hensel, 1955 and others). Following recovery from acute severe overheating in the course of several hours and even days, disturbances of general thermoregulatory reactivity appear, as well as problems with metabolism and other vegetative functions. Individual cases of subsequent death and development of acute psychoneurological symptoms occurring several days following recovery from heat stroke have been described.

Under conditions of a hot climate and intensive insolation the phenomena of overheating may occur, resembling heat stroke or sunstroke. The pathogenesis of these two pathological states is not the same and we now know a number of factors that make it possible to distinguish one from the other. /206

The first description of heat stroke is attributed to the military physician Horn who observed cases of overheating during hot weather on a march in 1760. The soldiers displayed paleness of the skin, their pulse had speeded up to twice normal, loss of sensitivity became evident, and then epileptiform fits developed, after which death rapidly ensued. Hiller (1902) mentioned general muscular weakness and weakness of the heart muscle as the precursors of heat stroke. Exhausted respiratory muscles are in no condition, in his opinion, to satisfy the oxygen needs of tissue. These phenomena, which appear prior to the development of heat stroke, Hiller called in German, "Marschonmacht", in other words, "collapsing on the march". After studying 558 cases of heat stroke, the author distinguished between the following forms: 1) asphyxic: the patient shows increased perspiration, weakness and dizziness; respiration becomes frequent and shallow; simultaneously, there is a slackening of cardiac activity, and symptoms develop that are reminescent of those of oxygen insufficiency (cyanotic shadows on the cheeks and lips); later the production of perspiration ceases and the skin becomes dry and hot to the touch; 2) paralytic or dyscrasic: this form is associated with a predominance of nervous disturbances, the development of spasmodic contractions of the muscles of the extremities, and subsequent opistotonus; the spasms develop periodically with pauses of 3-10 minutes; gradually the frequency and force of these spasms decreases, the pulse becomes imperceptible and respiration grows weak; 3) psychopathic form: in some cases, as the result of overheating, delirium, hallucinations and so forth develop. After recovery from the state of heat collapse, psychic disturbances may remain.

In 1956 Austin and Berry described 100 cases of heat stroke of which 70 involved persons aged 60 to 90. In all of the subjects, dry hot skin and reduced perspiration was observed, in 48% of the cases there were cardiovascular disturbances. In 56 persons, the body temperature was about 41° at the time of hospitalization; 98 persons showed disturbances involving the central nervous system, 4 were in a lethargic state and 53 were comatose.

In the opinion of F. G. Krotkov (1939), heat stroke is a typical disease, inasmuch as in the moderate European climate it is found primarily in troops during marches. Frequently the symptoms of heat stroke develop 6 hours after exposure to a high external temperature. In these cases, spasms of an epileptic nature are observed, delirium, symptoms of paralysis and disturbances of speech.

Sunstroke develops under the influence of solar radiation on the exposed head, especially when doing heavy muscular work. It is accompanied by headache, decrease in strength, reddening of the face and loss of consciousness (I. Skvortsov, 1881).

G. Gurevich (1963) also describes the development of sunstroke. The patient develops fatigue, vomiting, disturbance of vision, general sluggishness, reddening of the face, increase in body temperature (up to 40°), speeding up of pulse and respiration. Later loss of consciousness occurs, and body temperature reaches 42-44°. Breathing remains accelerated, but regular; however, after a short time it becomes Cheyne-Stokes and in serious cases stops, due to paralysis of the respiratory center. The pulse, initially accelerated, slows down, becomes stressed and weakens due to the drop in cardiac activity; there is a drop in the arterial pressure. Production of sweat stops. Hemorrhages occur in the brain and internal organs. Damage to the central nervous system takes place in the form of development of drowsiness, a dreamlike state, clouding of consciousness and frequently spasms. General excitation, hallucinations, and feelings of horror and delirium develop in other cases. /207

The difference between heat stroke and sunstroke must be considered in the light of the fact that in the former there is a general overheating of the body, while in the second the primary cause is overheating of the head by the hot rays of the Sun. Many authors do not subscribe to the division of heat injury into heat stroke and sunstroke, since in their opinion there is insufficient basis for this (F. G. Krotkov, 1939 and others). In addition, no one will dispute the view that sunstroke is a consequence of primary damage to the central nervous system caused by intensive or prolonged action of direct solar radiation on the area of the head. Naturally, there is a general overheating of the organism (K. Aratskiye, 1931; N. N. Kalitin, 1934 and so on).

According to the experimental data, animals that are in the Sun develop the symptom complex of pathological phenomena whose cause lies in the action not only of the Sun's rays on the head but also the heat rays and the convection of heat from the external environment to the entire organism. The process that develops as the result of these disturbances may be referred to as solar-heat overheating (A. Yu. Tilis, 1947). The study of its development under conditions of exposure of dogs in a sunny area on a short chain (60-80 cm) with an air temperature in the shade of 35.8-36.2° showed that (judging by the external developments) the picture of such overheating in animals can be divided into three periods.

During the first period, there is no characteristic reaction involving the animal at all. This period is "indifferent" and lasts about 5 minutes, rarely 10-15 minutes. Then the second period of overheating begins -- the period of excitation. Respiration speeds up to 200-250 breaths per minute. Restlessness of the animal increases steadily. The body temperature rises. The pupils dilate, reflexes increase and the dog responds to a call. Following the period of excitation, there is a measure of calm. The animal is less excited but the body temperature continues to rise. The respiration slows down somewhat. The third period of overheating begins. The dog does not respond to a call, and does not react to the environment. Reflexes, with the exception of the corneal reflex, are absent. Breathing becomes more and more infrequent. Muscle tone weakens. The dog cannot move around independently. Later, spasms develop. Breathing becomes rare, irregular and then stops. After several seconds (10-70) the heart stops as well.

As we have already pointed out, under conditions of exposure to a hot environment the heat production initially increases, leading to further rises in body temperature (Lind, Hellon, 1957; Cranston, Gerbrandy, Snell, 1954; Belding, Hertig, 1962). However, in some cases during the first few minutes (thanks to increased functioning of the regulatory mechanisms) there is even a slight decrease in body temperature (Ye. B. Babskiy, A. Kh. Petrachev, 1934; M. Ye. Marshak, V. G. Davydov, 1927; N. V. Danilov, 1941 and others). A similar phenomenon occurs at normal environmental temperature with conditioned reflex evocation of reactions of heat loss (P. N. Veselkin, 1945 and others).

In our experiments (A. Yu. Tilis, 1950), when the dogs were placed in a sunny area, the body temperature rose during the first few minutes. Using this indicator, we can distinguish three periods between solar-thermal overheating. The first period involves rectal temperatures from 37.8-38.5° increasing to 40-40.5° at an average rate of about 0.5° per 10 minutes (37 minutes on the average); the period lasts from 25 to 55 minutes; the second period involves /208
an increase in body temperature from 40-40.5° to 42-42.2°. It lasts from 35 to 212 minutes (90 minutes on the average). The body temperature during this period increases very slowly (by 0.23° per 10 minutes on the average). The third period is marked by an increase in body temperature to 43-44° or more; it lasts from 10 to 55 minutes (31 minutes on the average) with a rate of temperature increase of 0.72° per 10 minutes. The total duration of the solar--thermal overheating form the beginning of exposure to the death of the animal is 158 minutes on the average (with individual variations from 70 to 320 minutes).

In our opinion, it is the rate of increase in body temperature which most objectively reflects the dynamics of the development of solar-thermal overheating by periods, which do not agree completely in time with the development of clinical symptoms. Usually the changes in the composition of the blood, its biological properties, the magnitude of arterial pressure and other hemodynamic and biochemical changes follow an increase in body temperature.

Pathological Physiology of Changes and Their Pathogenesis

Circulation of the Blood

The most constant symptom of incipient overheating is acceleration of the rate of cardiac contractions. In a man subjected to the action of heat, the frequency of the cardiac contractions can reach 115-138 beats per minute (Dutkiewicz, 1956). In the mechanism of development of tachycardia, heating involves factors and reflects effects involving the vessels and other organs.

The majority of authors have observed an increase in the minute volume of the heart under conditions of overheating (Koroxenidis, Sheperd, 1961; Kaufmann, Hundeshagen, Schlitter, 1960). This increase was observed by M. Ye. Marshak (1926) in persons under conditions of a high ambient temperature only with disruption of processes of thermoregulation. In the opinion of the author, it is due to redistribution of blood, decreased filling with blood and smaller blood supply to the internal organs, with the blood being sent to the periphery of the body. In the opinion of A. M. Blinova (1934), the minute volume

of the heart increases only during the first period of heating. With a further increase in temperature of the body, there is a decrease in the work of the heart.

According to our data, in the case of solar-thermal overheating at the beginning of the first period the minute volume of the heart increases 1.5-2 times. In the second period, the cardiac output drops 12% and in the third period it is only 1/5 or 1/2 of its initial level. These results indicate extreme exhaustion of the entire cardiovascular system (A. Yu. Tilis, 1964).

A drop in arterial pressure under the influence of overheating was also pointed out by Bernard. Under natural conditions of a hot climate, the arterial pressure increases slightly at the beginning of the first period of solar-thermal overheating (N. V. Danilov, 1941). Hypertension is caused by an increase in the volume of circulating blood (M. Ye. Marshak, 1926; W. Borchardt, 1930; A. M. Blinova, 1934 and others), acceleration of the blood flow and an increase in cardiac output. Insignificant venous hypertension also becomes characteristic of the initial period of overheating (A. Yu. Tilis, 1949), which may be viewed as a consequence of the increased influx of blood to the heart (G. A. Malov, 1932). At the beginning of the second period of overheating, arterial pressure begins to drop to 87 ± 2.7 on the average instead of the original 119 ± 2 mm Hg. In the third phase it gradually drops all the way until the animal dies (A. Yu. Tilis, 1964). S. B. Fabrikant, Sh. A. Aliyev /209
and O. Sh. Shaimbetov (1963) also showed that in dogs in a heat chamber, with an ambient temperature of 45-48° the arterial pressure remains surprisingly constant for a long time (4-5 hours) and it is only 30-45 minutes prior to the death of the animal that it gradually drops.

It may be said with sufficient accuracy that the decrease in the arterial pressure during overheating involves vasodilation. This mechanism forms the basis of the slight arterial hypotension described by many authors in the inhabitants of hot countries (G. F. Lang, 1929; M. I. Slonim, 1939; A. A. Kaplan, 1934; E. I. Umidova, 1949; S. R. Dikhtyar, 1941; V. K. Solov'yev, 1934; N. T. Tsishchnatti, 1959; A. Yu. Tilis, 1960, and others).

With the development of overheating, primary significance is attached to the slackening of the function of the myocardium. We know that there is a rise in venous pressure when the contractile ability of the heart muscle decreases. This is precisely why there is an increase in venous pressure in the second period (115 ± 0.8 instead of the original 59 ± 0.3 mm Hg), while the arterial pressure begins to drop (A. Yu. Tilis, 1964). Similar data were obtained by Schlitter et al. (1960). They showed that prolonged exposure of healthy persons to a heat chamber causes a drop in arterial pressure, while the venous pressure increases under hot conditions.

The slackening of the function of the myocardium with overheating is caused by disruption of coronary circulation (A. V. Vasil'yeva, 1962; N. V. Alisheyev; D. A. Koksharov and others, 1959; Terranava, 1953 and others). In addition, an important role is played by the accumulation in the blood of biologically active substances which have a toxic action on the heart muscle.

Finally, there is exhaustion of the reserve forces of the heart, and cardiovascular insufficiency develops.

Respiration. Disturbance to respiration during overheating, as we have already pointed out, is sharply different in the two groups of mammals. One group of mammals has no sweat glands and regulates heat loss by evaporation through the polypnoeic reaction (usually well-developed in predators). The other regulates heat loss by evaporation of the sweat that it produces (marsupials, primates, man). Acceleration of respiration during overheating is comparatively slight in the latter and its role in increasing heat loss is insignificant (D. A. Shevelyukhin, 1934; A. D. Slonim, 1962).

Polypnea, as a complex specific thermoregulatory reaction, involves a sharp increase in respiration (up to 200-300 breaths per minute or more), opening of the mouth and liberal secretion of thin watery saliva. Applying any mechanical obstacle to breathing, including muzzling the dog, impedes the development of polypnea and leads to very rapid overheating of the animal when the latter is exposed to the Sun or to a hot chamber. Breathing air with 10-15% CO_2 prevents development of polypnea during overheating, and interrupts and alters the rhythm and depth of respiration during dyspnea (Garrelon, 1909; Anrep, Hammouda, 1933; Alberts, 1961 and others). The central pulse mechanism of the reaction of polypnea has to do with the thermoregulatory centers of the hypothalamus; in the decerebrate dog, following cutting of the brain stem or destruction of the hypothalamus, there is only a nonspecific acceleration of respiration (up to 80-40 per minute) (Bazzlt, Penfield, 1922; Sherrington, 1924; Hammouda, 1933 and others). Thermal polypnea develops quickly in dogs. Depending on the degree of overheating, the respiratory rhythm initially rises to 80-90 times a minute and then suddenly reaches 200-250-300 or more per minute and is accompanied by opening of the mouth.

The question of the triggering mechanism for the polypnoeic reaction at /21
high ambient temperature has been discussed in the literature for a long time. As is the case for other thermoregulatory reactions, we can speak of a relative significance of peripheral extro- and interoreception and direct temperature influence on nerve centers. More detailed studies in recent times leave no doubt that the local increase in brain temperature in the vicinity of the anterior hypothalamus by 1.5-2° causes polypnea even at normal ambient temperatures. At the same time, the ambient temperature has a considerable influence on the intensity of the polypnea with standard local heat or electrical stimulation of the brain. At low ambient temperature, "central" polypnea develops with difficulty; when it is high, the latter develops very easily (Anderson, Persson, 1957, 1960 and others). At the same time, during external heating, polypnea develops before the ambient temperature rises, as well as the temperature of the blood and brain (Richet, 1886; Thauer, 1939, 1943; P. N. Veselkin, 1945; Bligh, 1957 and others).

Hence, the information reaching the brain from the external and internal environments plays a role in the triggering of the heat liberation reaction. The interaction between the extero- and interoreceptive signals may be accomplished in different ways, depending on whether exogenic or endogenic

overheating factors predominate in a given case. Thus, for example, Lim and Grodins (1955) have shown that the fatigue produced by general overheating of the body ceases with isolated cooling of the trunk to 38° or a drop in brain temperature to 38-39°. The inhibition of heat fatigue with local brief exposure to cold on the skin and mucous membranes indicates the importance of the role played by peripheral nerve endings in the development of this reaction (P. N. Veselkin, 1938, 1945).

It is characteristic that puppies, particularly during the first few days of life, due to the incompleteness of their development of nervous mechanisms of thermoregulation, do not respond to thermal stimulus by thermal polypnea (O. Ya. Ravikovich, 1954; P. M. Gan, 1958 and others). They are also incapable of developing fevers under the influence of infectious stimuli. On the other hand, in mature animals (for example, guinea pigs) the thermoregulation reaction is completely adequate even during the first few days of life (Ye. Shevel'ko, 1967).

In dogs kept in a sunny area, thermal polypnea develops instantaneously and lasts for the entire second period of solar-thermal overheating. The development of the third period is accompanied by a similar instantaneous transition of the respiration type to a slower variety (although somewhat accelerated in comparison with normal). Subsequently, the rate of respiratory movement gradually slows down, respiration ceases and terminal respiratory movements develop after 30-45 seconds have elapsed. Cardiac activity ceases somewhat later.

Blood gas composition. The data in the literature on blood gas composition under the influence of heat and solar radiation are quite inadequate. Garrelon (1909) was the first to establish that in the case of overheating during the period of development of thermal polypnea in dogs the oxygen content in 100 ml of blood increases from 18 to 23 ml, and the CO_2 content drops from 44 to 34 ml. Arterialization of the venous blood in overheating has been observed in human beings in a warm chamber and under conditions of hot work areas (Ye. F. Georgiyevskaya, G. V. Dervie, O. F. Zavalishina, 1934; H. F. Pyasetskiy, 1930; Ye. M. Brusilovskiy, G. S. Lur'ye, 1927 et al.). Following one and one-half hours of exposure to the Sun under conditions of a hot climate, oxygen capacity and the amount of oxygen in the arterial and venous blood increases somewhat according to the observations of A. Kh. Khodzhayev (1954).

According to our observations (A. Yu. Tilis, 1961), during the first 10-20 /21
minutes of exposure of animals in a sunny area there is a noticeable decrease in the oxygen capacity of the blood (by 0.8% by volume on the average) and a slight decrease in the oxygen content in the arterial blood. In contrast to this, the venous blood shows an insignificant but regular increase in oxygen content (from 65.3 to 69.6%). Some arterialization of venous blood is apparently a reflection of acceleration of the linear and volume rates of blood circulation during the first period of overheating.

Subsequently, in conjunction with the developing disturbance of blood circulation and the development of stagnation phenomena, the oxygen content in the venous blood drops progressively, reaching 5.6% by volume during the third period of solar-thermal overheating. In addition, the oxygen capacity increases steadily (up to 21.1% by volume) in conjunction with the increase in the amount of hemoglobin (thickening of the blood). Regardless of this, the oxygen content in the arterial blood changes very insignificantly (Figure 50), which has to do not only with the disturbance of the operation of the circulatory apparatus but also with the relative insufficiency of respiratory function. With an increase in the symptoms of overheating and deterioration of circulation, there is a regular increase in the arteriovenous differential with respect to oxygen content (up to 7.4% by volume in the second period of overheating and up to 11.9% by volume in the third). At the same time, there is an increase in the degree of oxygen utilization (up to 68%).

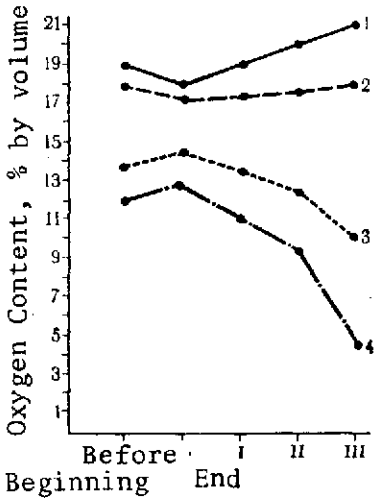

Figure 50. Dynamics of the Changes in Oxygen Content in the Arterial and Venous Blood During Various Periods of Solar-Thermal Overheating. 1, Oxygen capacity; 2, Oxygen content in the femoral artery; 3, Oxygen content in the jugular vein; 4, Oxygen content in the femoral vein.

An analysis of the changes in the gas composition of the blood shows that in the case of solar-thermal overheating changes occur in the oxygen budget of the organism which are characteristic of stagnation or circulatory hypoxemia, which is combined with the phenomena of hypoxic hypoxia.

Alkaline-acid equilibrium. Hypoxia and the disruption of metabolism during overheating has to do with the change in the reaction of the blood toward the acid side. The animals show an increase in the amount of lactic acid directly in the blood (G. V. Derviz et al., 1934; Ocamoto et al., 1955; Strzoda, 1958; Bianca, 1955) and in the muscle tissue (R. Ya. Yudelovich, A. M. Blinova, 1935) as well as in the cerebrospinal fluid (S. Ye. Severin, A. M. Blinova and A. G. Kozlova, 1934). The distortion of metabolism under the influence of high ambient temperature is accompanied by an increase in ketone bodies in the blood (Cali, 1961).

A decrease in the ability of the blood to bind CO_2 and a drop in reserve alkalinity may be explained in two ways: either overheating, regardless of increased excretion of CO_2 by the lungs (Danielson, 1938), involves accumulation of the acid products of metabolism (S. Ye. Severin, A. G. Kozlova, 1934; N. N. Meshkova, 1934; P. I. Fedorova, 1939; Adolf, 1938, et al.), or there is a decrease in the ability of the blood to bind CO_2 depending upon the transition of bases from the blood to the tissue (Flinn, Scott, 1922; Cayeli, 1956). /212

As indicated by our experiments on dogs, the alkaline reserve of the blood regularly decreases under the influence of solar-thermal overheating, reaching extremely low values during the third period (Figure 51).

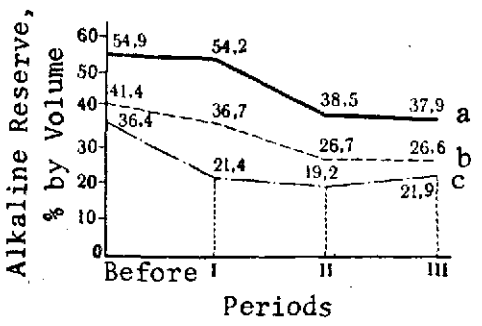

Figure 51. Alkaline Reserve of the Arterial and Venous Blood and Cerebrospinal Fluid With Solar-Thermal Overheating.
1, Cerebrospinal fluid; 2, Venous blood; 3, Arterial blood.

The decrease in the alkaline reserve of the blood during the first period of solar-thermal overheating must be linked to the development of thermal polypnea; in other words we are speaking of hyperventilation or gas alkalosis (Ch. I. Burshteyin, A. Yu. Tilis, 1956; Bianca, 1958; Albers, 1961 et al.). During the second period, in conjunction with progressive oxygen insufficiency, there is a gradual accumulation of the non-oxidized products of metabolism which interact with the bicarbonate buffer to cause a decrease in reserve alkalinity depending on the type of non-gaseous acidosis. However, inasmuch as thermal polypnea is maintained during the entire second period of overheating, there is a gradual development of a mixed form of disturbance -- gas alkalosis and non-gaseous acidosis. The decrease in the alkaline reserve to very low values, in the third period of overheating, nearly incompatible with life (15-18% by volume), leads us to consider this acute uncompensated acidosis.

Cellular Composition of the Blood. The first studies of heating of animals in a warm chamber showed a decrease in the number of erythrocytes in the peripheral blood (A. I. Ostapenko, 1882; S. I. Tvorkovskiy, 1900). The same thing happened in a warm chamber with human beings (Spealman, Newton, Post, 1947) and in workers in hot work areas (L. B. Feynberg, 1925; A. Ye. Byalokoz, 1936, and others). However, in the latter, there was an increase in hemoglobin and erythrocytes toward the end of the shift (Ye. A. Tsubenko-Tsubin and F. N. Gabuzoba-Tsubenko, 1927; M. S. Glekel', 1938; K. Yu. Yusupov, 1961 et al.).

The changes which develop have to do with a change in circulation, disruption of the function of the cardiac activity, the tone of the vessels (Winternitz, 1893) and the redistribution of the blood (S. I. Tvorkovskiy, 1900). In addition, A. K. Yegorov (1928), observing the action of solar radiation directly, observed a significant number of decomposing erythrocytes in blood smears. Recently, bilirubinemia and an increase in the qualitative reaction to urobilinogen have been observed (Ye. V. Kasatkin, 1935). Destruction of erythrocytes with simultaneous increase in hemoglobin has been also observed by A. S. Shatalina (1935) following 4 hours irradiation of animals in a sunny area. Disruption of erythrocytes is a function of the

intensity of solar radiation, the quantity of infrared radiation, the duration of the animal's exposure in the sunny area and the time of day (A. A. Sarkisyan, 1954).

I. A. Kassirskiy (1948) has shown that under high temperature conditions, as a result of a slight initial dilution of the blood, there is an initial decrease in the number of erythrocytes, followed by thickening of the blood. /21
Similar data were obtained by A. Yu. Yunusov (1961) in experiments on dogs, following 2 hours exposure to sunlight.

The effect of overheating on the blood was studied most thoroughly by M. Ye. Marshak and O. T. Dukel'skaya (1928). According to their data on healthy human beings placed in a warm chamber, the first period of heating is accompanied by a decrease in the number of erythrocytes, the amount of hemoglobin and the viscosity of the blood. Beginning with the second hour of exposure to the chamber, there is an increase in the viscosity of the blood; the hemoglobin content rises, as does the number of erythrocytes.

In solar-thermal heating, the changes in the cellular composition of the blood in dogs, as indicated by our observations (A. Yu. Tilis, 1947) strictly follow the periods of development of the pathological process. During the initial phases of overheating, the number of erythrocytes decreases. Since there is a simultaneous drop in the content of hemoglobin and the dry residue of the blood during this period, we can assume that the dilution of the blood is an early reaction to the effects of high temperature. We cannot exclude the possibility that a decrease in hemoglobin level under conditions of a hot environment has to do with a redistribution of fluid in the tissues when an increase in extracellular water in the blood and lymph takes place (M. A. Khvoynitskaya et al., 1951; Scheid, 1956) and there is a transfer of fluid from the tissues to the vascular bed. In fact, in the case of overheating, the skeletal muscles and skin release the water which is stored in them (M. G. Mirzakarimova, 1958, 1961). Dehydration of the cells by 0.4-2.9% and an increase in the extracellular fluid volume by 0.7-2.3% under the influence of high environmental temperature on human beings under conditions of complete rest was observed by Frada and Mentasana (1960) and others. The dilution of the blood during the initial phases of overheating must be viewed as a special form of accommodation of the organism, inasmuch as the mobilization of the water reserves which takes place during further exposure to high temperature and insolation ensures the most rapid triggering of the basic mechanisms of heat liberation through evaporation (polypnea in dogs, perspiration in man).

During the second period of solar-thermal overheating, with an increase in body temperature to 41.7-42°, thickening of the blood develops. The dry residue of the blood increases, as does the hematocrit, the number of erythrocytes and the hemoglobin content. Fluid losses associated with the stress of thermoregulation lead to anhydremia and an increase in the number of formed elements of the blood per unit volume.

During the third period of overheating, thickening of the blood increases. However, the number of erythrocytes and hematocrit decrease in comparison with the second period, almost to the original values. This indicates partial hemolysis of the erythrocytes, since a decrease in their minimal resistance occurs during this period.

As far as the white blood is concerned, under brief exposure to solar radiation (10-40 minutes), while taking sunbaths (G. V. Sirotinin, 1927; Schreiber, Spode, 1954) or during the initial period of overheating (S. L. Zel'kin, 1910; B. H. Erschoff, Gaines, 1953; A. M. Zubov, 1902; L. A. Nikol'skaya, 1925; Chopra, 1938) there is a decrease in the number of leukocytes. Evidently this leukopenia is of a redistributory nature (I. R. Bakhromeyev, 1936; A. I. Mikrin, L. M. Rakhlin, 1923; Mueller, 1922 et al.) and has to do with a change in the tone of the peripheral vessels. Possibly this is linked to the decrease of the amount of white blood elements which has been observed by many authors to take place in summer in the inhabitants of hot countries (O. N. Pavlova, 1939; M. L. Mgebrov, 1936; I. G. Mardershteyn, 1936; S. D. Kalenova, 1956; Gensslen, 1937 et al.) and a change in the leukocytic formula. At the same time, the number of lymphocytes in the blood increases (Kennedy, Mackay, 1936; Suarez, Mandray, 1934; M. L. Mgebrov, 1936; A. Kryukov, 1929; I. A. Kassirskiy, 1935; S. D. Kalenova, 1956; O. N. Pavlova, 1939). With prolonged exposure to heat or solar radiation, the number of leukocytes gradually increases. This process can be observed in workers in hot areas as the result of thickening of the blood. /214

In workers who are in a sunny area, during the second hour of exposure to high temperature, one can already see a slight increase in the number of leukocytes (A. Yu. Yunusov, 1961). In addition, it is not possible to detect any qualitative changes affecting the white blood, and the leukocytosis which develops in the course of the second period of overheating must be considered redistributory. During the third period of solar-heat overheating, the number of leukocytes continues to increase; simultaneously, there is a regenerative change in the blood formula toward the left, all the way to the development of juvenile cells, i.e., true leukocytosis develops (A. Yu. Tilis, 1960).

Water-salt exchange. Maintenance of homiothermia under conditions of high ambient temperature, as we have already mentioned, is totally dependent upon the increase in heat output by evaporation. Ensuring evaporation of the water on the surface of the body (physiological mechanisms) during overheating continues to function intensively almost up to the preagonal period. The loss of fluid associated with this may reach 1.5-2 and even 3.5 kg/hr in man, which is easily compensated by a decrease in the body weight (M. Ye. Marshak, L. M. Klaus, 1927; V. I. Magnittskiy, 1934; Adolf, 1938; Dutkiewicz, 1955; Gibinski, Giec, 1958; Ahlman, Kavonen, 1961 et al.). Experimental studies have shown that the maximum stress on sweat excretion (as evaporation through polypnea) may be caused by high temperature of the environment even at rest. However, in conjunction with muscular work, the maximum stress on sweat production develops much more rapidly and at lower environmental temperatures (Kuno, 1961; V. K. Solov'ev, 1934; V. I. Magnitskiy, 1934 et al.).

Since a certain amount of mineral substance is lost with the perspiration, saliva and secretions of the mucous membranes (especially sodium chloride), intensive sweating and polypnea involve disruption of the salt composition. Losses of sodium chloride in man can reach 25-30 grams per day (M. Ye. Marshak and L. M. Klaus, 1927; N. German, 1933; A. Savel'ev, 1929; Carnazzo, 1953 et al.). Loss of chlorides during overheating is observed in animals as well, so that their content in the blood drops (G. V. Derviz et al., 1934; Pincussen, 1925, 1927; Macriones, 1925 et al.). Under industrial conditions, Yu. M. Gefter and F. Ya. Yudelovich (1931) observed a drop in the number of chlorides in the blood from 440.6 to 412 mg % in stokers during cleaning of furnaces. It is precisely the decrease in the content of sodium chloride in the blood and tissues that we frequently link with the spasms that are observed in workers at steel-casting plants (Talbot, Dinn, Edwards, 1937; Oramo, 1960). Ito, Masui, Khattori et al. (1942; cited in Kuno, 1961), working with healthy human beings, showed that a loss of 8.8 grams of chlorine with the sweat meant that its content in the blood did not change or merely dropped slightly. In the opinion of Kuno (1961), since the chloride content in the perspiration was low, dehydration could not decrease (but increased) its content in the fluids of the organism; if this did not take place, it was only because of the triggering of regulatory mechanisms, particularly the increased excretion of chlorides with the urine. Changes in chloride content of the blood during overheating are governed by a number of conditions, particularly the nature of the previous nutrition (E. S. Belova, 1961). Thus, following a two-hour /215
insolation, animals on a mixed diet showed a drop in the chloride content in the blood; with a predominantly protein or carbohydrate diet, they showed an increase (M. V. Abduamatova, 1961).

Our studies indicate that in the case of solar-thermal overheating the chloride content in the blood and cerebrospinal fluid decreases regularly. During the initial stages of overheating, this decrease is insignificant, but at the end of the second period the chloride content in the blood drops by 23% (and in the cerebrospinal fluid by 19%) of the original level. The drop in the chloride level is still more pronounced during the third period of overheating (by 25.7 and 22.2% respectively). Significant chloride losses, not only in the blood but in the cerebrospinal fluid, indicate a disruption of the permeability of the hemato-encephalic barrier, so there is apparently a drop in the cerebrospinal pressure with pronounced symptoms of solar-thermal overheating (A. Yu. Tilis, 1964).

Many authors link the changes that occur during overheating (with respect to the ionic balance of the blood) with the development of certain symptoms of thermal exhaustion. Thus, Knochel et al. (1961), have described a case of heat stroke which was complicated by myocardial infarct, and pointed out the significance in the pathogenesis of this symptom complex of an inadequacy of potassium ions in the organism due to their increased excretion by the kidneys. In contrast to this, Frada and Mentasana (1960) and Fuyito (1956), found a significant increase in potassium content (by 11%), of high ambient temperature in human blood serum under conditions especially after muscular stress. The hyperkaliemia which develops during overheating was viewed by Carnazzo (1953) as a manifestation of increased activity of the adrenal cortex. However, V. D. Lindenbraten (1967), failed to observe any pronounced stress

reaction in moderate heating of rabbits and guinea pigs (by 1-1.5°). Activation of the adrenal cortex was observed only in more pronounced overheating. There are scattered indications of a decrease in inorganic phosphorus content in the plasma from 3.9 to 1.6 mg % (Kantor, 1960) as well as a tendency toward an increase in blood serum iron content (Salamone, 1953).

Hence, the pathological significance of the changes in the physical--chemical composition of the blood which takes place during overheating has been insufficiently explained.

Carbohydrate, nitrogen and protein metabolism. In the overheating of animals in a hot chamber (Flinn, Scott, 1922), as well as after insolation in summer (Ocamoto, Ozuba, Nixon, 1955), an increased blood sugar level was found. A very pronounced hyperglycemia develops in dogs which receive a carbohydrate load on the day on which they were overheated (A. N. Kabanov, 1934). In addition, there are indications that the blood sugar level drops under the influence of high temperatures as the consequence of an increase in insulin content (N. B. Kozlov, 1955). A slight tendency toward a drop in blood sugar content following heating of the body in animals was observed by Scheid (1956).

In the case of solar-thermal overheating, the blood sugar level increases regularly (by 47.8% in the second period). However, there is an increase in the sugar content at the same time as hyperglycemia in the cerebrospinal fluid (A. Yu. Tilis, 1947). The mechanism of hyperglycemia has a complex origin. Here we must take into account the changes in the function of the vegetative nervous system and disruption of the state of the endocrine system, particularly the adrenals, accompanied by increased adrenaline production.

Apparently the hyperglycemia which develops during overheating has a significant influence on the resistance of the animal. Thus, when dogs were given glucose while in a warm chamber, A. N. Kabanov (1934) observed a decrease in the rate of development of overheating and a rise in the body temperature of the animal. According to the data of E. S. Makhmudov (1961) the temperature stability of the organism at ambient temperatures of 38-40° increases when a diet composed primarily of carbohydrates is given. /216

In his detailed work, published in 1901, S. Predtechenskiy observed an increase in protein breakdown during overheating of dogs, together with increased excretion of nitrogen products with the urine. Subsequent research has confirmed these data. However, several authors have obtained contradictory results (Linser, Schmidt, 1904; N. B. Kozlov, 1956; G. M. Zaynullina, 1950 and others). A more constant increase in the excretion of nitrogen products is observed at body temperatures above 40°, but no direct relationship between these changes and the degree of overheating has been observed; rather, it has been suspended by the action of other factors (Graham, Poulton, 1912-1913; I. S. Repin, 1961 et al.).

G. V. Derviz et al. (1934) observed that the onset of overheating was accompanied by an increase in residual blood nitrogen with a relatively slight increase in urea. Overheating is accompanied by increased excretion of amino acids with the urine (Ye. S. Novakovskaya, 1936), more nitrogen excreted with

sweat (A. A. Mittel'shtedt, Ye. S. Novakovskaya, 1934; F. A. Sverdlova, 1936), an increase in the residual blood nitrogen and ammonia (V. I. Panisyak, 1958), glutamine and other products of the breakdown of protein (N. B. Kozlov, 1958; I. V. Drobintseva, 1958; V. A. Pegel' and G. M. Zaynullina, 1960).

As far as changes in the protein content and in its fractions is concerned, according to the research of F. V. Voskresenskiy (1934) all cases without exception indicated that overheating is accompanied by an increase in albumin fractions in the blood. The content of globulin fractions and fibrinogen decreases. Borchardt (1930) links the increased protein content in the plasma with the entry of protein-rich fluids from tissues into the blood. Disturbances of protein content in the plasma under conditions of hot moist air were observed by Lampierto, Mager and Graen (1961) and others.

In our observations involving solar-thermal overheating, there was an initial decrease in the total blood serum protein content. However, by the end of the first period of overheating the protein level reached the original values (8.2-8.3%). In the middle of the second period the serum protein content increased up to 8.8-8.9%, reaching a maximum in the third period (9.4-10.2%). The changes observed in the blood protein composition are evidently linked to the onset of blood thickening (A. Yu. Tilis, 1964).

Function of Digestive Organs. One of the characteristic features of overheating in animals which do not possess sweat glands is increased salivation. At a temperature of 40° salivation began 15-30 minutes following the start of the experiment, and considerably earlier when the ambient temperature was higher (Ye. B. Babskiy and A. Kh. Petrachev, 1934). The viscosity of the secreted saliva decreased simultaneously with the increase in its quantity (Richet, 1889; R. B. Garib'yan, 1953; T. I. Danilova, 1951); its chloride content decreased by nearly a factor of 2, and a slight increase in the calcium content was observed. In cases of repeated overheating, salivation and the degree of modification in saline content of the saliva became more pronounced, indicating the development of adaptational processes under these conditions (Z. T. Tursunov, 1961; A. Yu. Yunusov and G. F. Korot'ko, 1962). The majority /217
of authors mention an inhibition of the secretory function of the stomach under the influence of overheating. Exposure of dogs to a warm chamber at 45° causes a significant inhibition of the first reflex phase of juice secretion, a somewhat reduced inhibition of the second, and considerable distortion of the secretory curve (N. I. Putilin, L. N. Staritskaya, 1955). Under conditions involving overheating of dogs in a light-air chamber with increased body temperature over a 2-hour period by 1° on the average, there is a lengthening of the latent period of juice secretion, a decrease in the acidity of the juice (due to free hydrochloric acid) and its digestive power, and an increase in dry residue (M. M. Dzhalilov, 1958).

Similar data were obtained under industrial conditions, involving human beings exposed to high temperatures (D. A. Shevelyukhin, 1929) and under experimental conditions involving an artificial tropical climate (Borchardt, 1930). The degree of reduction of secretion during overheating is also a function of the duration of exposure to high temperature (A. Yu. Yunusov, G. F. Korot'ko, 1962).

Under the conditions of a hot environment, the total nitrogen and urea content in the gastric juice increase; this may possibly be related to an inhibition of renal activity. We cannot exclude the possibility that increased concentration of nitrogenous substances in the gastric juice is due to an increase in the permeability of the gastric tissue and the capillary walls. In fact, under the influence of high ambient temperature and solar insolation, the porosity of the capillaries increases as the symptoms of overheating become more acute (F. F. Sultanov, 1958).

Overheating is accompanied by changes in the motor function of the stomach. They take the form of a prolonged disappearance of periods of contraction, lengthening of the periods of rest of the empty stomach, and a decrease in the duration of the periods of contraction (Ye. B. Babskiy, 1934). In other words, there is a decrease in the tone of the gastric musculature and in the inertia of the motor apparatus.

With respect to the mechanism of the changes in the motor and secretory activity of the stomach, the inhibition of the digestive center is of particular importance; this is caused by sterilization of the thermoregulatory center (A. Yu. Yunusov, G. F. Korot'ko, 1962). An important role in this process is also played by the sympathetic branch of the autonomic nervous system, whose tone increases when the organism is exposed to high temperature (Gellhorn, 1955). It is also necessary to take into account the changes in circulation, particularly the decreased blood flow to the stomach and other organs of the digestive system.

Under the influence of high temperature and insolation, the secretory activity of the liver, pancreas and intestinal glands is inhibited. The rhythm of secretion of bile changes, and there is a marked decrease in its secretion in response to food stimuli -- meat, egg yolk, and milk (M. V. Konstantinov, 1958). A decrease in the amount of intestinal juice is accompanied by a rise in its chloride and sodium concentration and a decrease in the calcium content. At the same time, there is a decrease in the enzyme content in the intestinal juice, particularly in the case of enterokinase (D. I. Bel'chenko, 1958). The volume of pancreatic juice decreases markedly during overheating; it becomes thin and filled with mucus, and there is a decrease in sodium content, while the chloride concentration increases. Inhibition of the pancreas is more pronounced in the reflex phase of juice secretion (G. F. Korot'ko, 1958, 1959).

After-Effects of Acute Overheating

The question of the nature of the reactions of the organism during the posthyperthermal phase, which develops following heat stroke, is of great interest. /218

The experiments that have been performed in this area have shown that cessation of exposure to heat is followed by phenomena of an aftereffect, when the functions of many systems remain disturbed for a period of time. According to the data of T. A. Salavaya (1958) the rectal temperature of dogs, after they have been exposed to a chamber at 45-50° for 50-60 minutes, only

returns to its original level 40 minutes following exposure to heat. Frequently, restoration of rectal temperature is observed only on the second or third day following overheating (S. I. Burikhanova, 1967). In addition, the functional state of the thermoregulatory centers, even after normalization of body temperature, remains somewhat disturbed. Thus, during the aftereffect period the shape of the temperature curve (in response to the administration of pyrogens) resembles that of the type of reaction which may be caused in an intact animal by the administration of excessive doses of pyrogen (F. F. Sultanov, 1965).

The return of body temperature to the initial level is not accompanied by restoration of circulatory function, gas exchange, the blood system and the activity of other systems to normal. Thus, in 1937 A. D. Slonim and O. P. Shcherbakova noticed decreased metabolism in dogs and monkeys after they had been overheated for 5 days. In further experiments (1938) the authors noted that monkeys maintained a reduced oxygen consumption level for 5 to 8 days following prolonged overheating.

Aftereffects of exposure to acute overheating also come to light when the acid-alkali equilibrium is examined. According to the data of G. Kh. Shakhbazyan and F. M. Shleyfman (1959), the amount of sugar and reserve alkalinity of the blood are considerably below the original values on the 5th through 10th days following an experiment. Even on the 15th to 20th days these changes still persist. Plasma alkalinity remains below the original level even on the 30th day following the end of the experiment. It is worth noting that the increased vascular-tissue permeability of the internal organs, skin and brain, which is characteristic of overheating (F. F. Sultanov, 1965), is retained for a long time following exposure to heat.

The decrease in gastric secretion, the reduced acidity of the juice and the inhibition of gastric motor functions in individuals or animals exposed to overheating persists for 12-16 days (M. D. Eydinova, 1934 and others). The digestive power of the gastric juice initially remains low and returns to normal much later (E. G. Zakharova, 1962). It is interesting to note that the process of restoration of functional activity of the gastrointestinal tract is largely dependent upon the degree of overheating. Thus, following a single case of acute overheating the aftereffects last 7-10 days, while multiple overheatings are followed by aftereffects lasting 15-20 days (O. F. Sharovatova, 1938).

Usually a decrease in the quantity of hemoglobin and erythrocytes is observed in dogs for 8-10 days following exposure to high temperature. The anemia which develops is the result of hemolysis under the influence of toxic metabolic products, even when the direct influence of the temperature factor is absent (O. Sh. Shaimbetov, 1966). Delayed maturation of the erythrocytes during this period is associated with inhibition of the function of the hemopoietic system, caused by the marked inhibition of the hemopoietic activity of /219
the blood serum (S. B. Fabrikant, 1967).

In response to a two-hour exposure to high temperature and insolation, animals continue to show prolonged aftereffects which consist in changes in

the gas exchange and thermoregulatory parameters. On the basis of observations conducted 25-30 days following overheating, S. I. Burikhanova (1967) divided the aftereffects into three phases on the basis of the nature of the changes which occur. In the first phase there is an increase in oxygen consumption, increased heat production with high pulmonary ventilation, and a slight increase in body temperature. This phase lasts from several hours to 5 days. In the second phase of aftereffects, oxygen consumption drops, heat production decreases, pulmonary ventilation is only about 65% of the original level, and the body temperature falls. The respiratory coefficient reaches very low values (0.65-0.58). This phase lasts 10-15 days following overheating. During the third phase there is a slow recovery of gas exchange and thermoregulatory processes which ends only 25-30 days after exposure to overheating.

These functional changes during the aftereffect period combine to reduce significantly the general (nonspecific) resistance of the organism. During the first few days following overheating, the animals become very sensitive to various pathogenic influences. As far back as 1946, I. R. Petrov pointed out that the lethal blood-loss volume for animals in Samarkand on hot days was much less than in Leningrad. Later, O. Sh. Shaimbetov (1965) showed that even a slight loss of blood (2% of body weight) in animals following recovery from the initial period of solar-thermal overheating is accompanied by a more pronounced decrease in arterial pressure (by 70%) than accompanies the same blood loss in winter. More than half the animals in these instances perished during the first few days following the tests. Against a background of preliminary overheating, loss of 2% of the blood causes prolonged periods of anemization with a more pronounced decrease in the quantity of hemoglobin than is the case for the controls (by 42.5% instead of 25.8%). The recovery time of the hematological parameters in such animals is retarded by almost 1.5 to 2 times (V. I. Kalugina, 1968).

Burn shock has a serious course under aftereffect conditions. Burns over 18-20% of the total body surface, which are relatively well tolerated by dogs, cause shock terminating in death in all instances in animals that have been subjected to solar-thermal overheating.

Methods of Prevention and Therapy

Adaptation plays an important role in preventing overheating. This is why a gradual transition from a low (31.3-32°) ambient temperature to a high one (41.7°) produces a less pronounced increase in body temperature and increases labor productivity (Wyndham, Strydom, Morrison, 1954; Harrison, 1958; Bean, L. W. Eichna, 1944; Wyndham, 1954; Hensel et al., 1955) and in animals (Harrison, 1958) promotes a higher survival rate and resistance to overheating. Higher resistance to the effects of high ambient temperature can be achieved by training under hypoxic conditions (Cheymol, Levassort, 1956; F. T. Agarkov, 1962; I. N. Blagoveshchenskaya, 1960; B. G. Marchenko and F. T. Agarkov, 1960; S. A. Pevny, 1957, 1960; N. I. Taranata, 1960). Thus, O. Sh. Shaimbetov (1965), who increased the resistance of animals under conditions of high-altitude and pressure chamber hypoxia, achieved increased resistance stimultaneously with respect to overheating and blood loss. /220

Observation of a strict diet is of great importance in the prevention of overheating, particularly when working in hot shops. It is necessary to consider that during exposure to heat stress, simultaneously with intensive perspiration (salivation in animals) the organism loses a great deal of sodium chloride. In this connection, the choice of diet must provide for maintenance of the sodium-water balance of the organism (M. Ye. Marshak, 1926; O. P. Molchanova and Ye. N. Yezhova, 1935; B. A. Krivoglaz, 1952; G. A. Vladimirov and Ye. Ya. Geyman, 1952; A. Yu. Yunusov, 1960; K. Yu. Yusunov, 1960).

As far as problems of therapy are concerned, we must take into account that dehydration of the organism affects man and animals during overheating and during the aftereffect period as well, with significant changes in mineral exchange, increased viscosity and decreased total circulating blood volume. Therefore, measures directed at replacing the lost fluid take on particular importance. A very favorable effect can be achieved by means of subcutaneous or intravenous administration of physiological solution, with chlorides being given simultaneously with the fluid. Talbott and Dill (1937) described the serious condition of 59 workers in hot shops located in steel-casting plants in the United States, who were taken to the clinic with symptoms of heat stroke. Administration of glucose, adrenaline, morphine, and a solution of calcium chloride failed to produce the desired effect, while intravenous administration of 900 ml of physiological solution immediately caused cessation of spasms in all the patients and led to a general improvement in their condition.

In view of the fact that an important role was played by the accumulation of products of a toxic nature in the pathogenesis of death from heat, an effective method of therapy might be the use of an operation involving replacement of the blood. In our studies (A. Yu. Tilis, 1968) this operation was carried out in two stages. We initially administered physiological solution (sodium chloride) in an amount which was equal to the total blood volume of the animal and then whole donor blood in the same volume. The fluid composition included glucose and cordiamine. This form of therapy, referred to as the operation of replacement of the blood by a "compound complex", was performed at 26-28°. Immediately following administration of the fluid, the rectal temperature of the animals dropped and remained low for the next hour. Breathing became less frequent, hemoconcentration disappeared, the protein, potassium and chloride levels in the blood plasma returned to normal, saturation of the venous blood with oxygen increased markedly, and the function of the cardiovascular system returned to normal.

Many authors (P. I. Yegorov, 1940; A. P. Fridman, 1936; G. Gurevich, 1935, 1963, etc.), among other first aid measures for sunstroke and heat stroke victims, recommend the use of lumbar puncture to reduce cerebrospinal pressure. A prerequisite for this intervention clearly must be pathomorphological data indicating that overheating has produced hyperemia of the cerebral vessels and meninges, as well as significant plethora of the veins and venous sinuses. In addition, direct measurements have shown that in the course of development of solar-thermal overheating the cerebrospinal pressure decreases regularly and becomes negative (A. Yu. Tilis, 1964). It should be pointed out that these changes occur in conjunction with a disruption of the water-salt metabolism, /221

which is observed in overheating and is the consequence of increased permeability of the hematoencephalic barrier.

During the last 15 years, moderate artificial overheating has been used with considerable success, together with fever, for therapeutic purposes (P. N. Veselkin, 1963). However, inasmuch as the functional disturbances that occur during overheating are of a rather serious nature, preference is given in the clinic to fever produced by slightly toxic pyrogens. Lipo-polysaccharide complexes of bacteria, given in negligible doses, produce a brief temperature rise in conjunction with their action on the corresponding thermoregulatory centers of the brain.

Conclusions

Overheating may be defined as a symptom complex of pathological phenomena associated with the accumulation of excess heat in the body and a rise in the temperature of the latter under conditions which are difficult as far as heat exchange is concerned, exceeding the physiological capacities of the body for maintaining heat loss at a level which is strictly adequate in terms of heat production. The pathological process that develops under these conditions leads to significant changes in the functions of many systems and organs and frequently places the organism in a situation which is incompatible with life. This is why the effects of high temperature in the environment must be considered extremal. The maximum stress is imposed on the function of the cardiovascular system and the thermoregulatory processes. Overheating results in a rise in body temperature, with phenomena of dehydration occurring as a consequence of water loss by the tissues; metabolic processes are disturbed, changes take place in the cellular composition of the blood, the function of the circulatory apparatus is impeded, and there is difficulty in respiration. After recovery from overheating, the phenomena associated with the aftereffects persist; they must be taken into account, particularly in those cases when it is necessary to handle aftereffects of a thermal nature. In these cases, there is a summation of the effects which frequently has a lethal outcome.

In the opinion of many authors, as a result of the action of the thermal factor, splitting of tissue proteins takes place (I. N. Matusis, V. P. Grachanovskiy, 1937), accompanied by increased formation of histaminoform substances, dermotoxins and necrohormones (G. D. Arnautov, 1935; Heilbrunn, Harris, 1946; N. T. Tsishnatti, 1959; Spurr, Bartow, 1959; V. A. Pegel', G. M. Zaynullina, 1960; O. Heroux, 1961 and others). The death of animals in overheating is associated with the symptoms of continuously increasing oxygen insufficiency.

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COLD TRAUMA

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Extremal states are possible both during frostbite and as the result of general cold trauma or freezing. In the latter, they are more probable and specific. /224

Extremal states in frostbite have a complex pathogenesis, governed by a specific syndrome and a septic state, frequently complicating the serious forms of frostbite. Hypothermia, employed in modern anesthesia, is theoretically distinct as a potential source of extremal conditions from the condition that exists in cold trauma. Its duration is measured in tens of minutes, rarely hours, while cold trauma and the extremal states producing it develop over 24 hours or more. Massive extremal states caused by general cold trauma are observed as a rule only in wartime. The freezing that took place among the French Army retreating from Moscow in 1812 is well known in this regard; we can also note the report by Kilian (1949) that during the winter of 1941-1942, a total of 19,000 officers and men suffering from cold trauma was reported among the German Army surrounding Leningrad. This form of trauma is encountered much more rarely in peacetime. Nowadays, under the living conditions that exist at the present time, this type of injury is observed extremely rarely, even in the Northern latitudes of the Soviet Union. Thus, during the 9 years since 1948 a total of only 12 persons have been recorded in Tomsk as suffering from acute cold trauma (V. N. Agafonova, 1963). Hence, under modern conditions cold trauma (particularly the general variety) occurs very rarely, almost exclusively in remote locations during disasters or during shipwrecks.

Pathogenesis of Cold Trauma

The extremal states involved in general and local cold trauma have a specific pathogenesis which is not duplicated in any other form of human trauma. The pathogenesis and pathological physiology of cold trauma are likewise specific. They have two periods of development which are basically different. During the first period of cold trauma, which has been conditionally named the "latent" or "prereactive" period, one can distinguish local and general hypothermia in which the mechanisms of thermoregulation are still retained. The second period is the second pathological phase of general hypothermia, characterized by disruption of the mechanisms of natural thermoregulation. In the case of local hypothermia, physiological thermoregulation is not disturbed and therefore the temperature inside the body of the individual suffering from external cold does not decrease. This period of homoiothermia in incipient general cold trauma is replaced by a period of poikilothermia. It is characteristic that even massive and serious freezing (frostbite) as a rule takes place without any clinical symptoms of freezing. In other words, loss by man and warm blooded animals of their biological homoiothermal capacity is limited to a comparatively few extremal states in general cold trauma. The transition to poikilothermia by warm-blooded animals and man which occurs in extremal states and is caused by cold trauma has been described in the literature of the last century, particularly by Bernard and other researchers. /225

On the basis of our own experiments and the data presented in the literature, V. N. Sheynis (1948) feels that the brain is in a favorable location to maintain constant body temperature longer than the other organs, i.e., it remains homoiothermal for a long time. Pathological-anatomical changes in the internal organs in general cold trauma, if death of the victim occurred during its initial period, are specific but scarce. In contrast to ordinary tissue and organ damage observed in lethal traumas and diseases of man, autopsy of frozen corpses shows only moderately pronounced morphological symptoms of hemostasis, hemorrhage and extravasation, which together do not explain the cause of death. Plethora observed in the tissues of the brain, liver, kidneys and spleen is supplemented by hemorrhages beneath the mucous membrane of the stomach, known in literature as "Vishnevskiy's spots". A. V. Orlov (1948) showed that the latter are observed in 60% of autopsied frozen corpses and may be viewed to a certain extent as being specific to general cold trauma. Inasmuch as general cold trauma takes place with obvious disturbances of the function of the brain and spinal cord, the attention of the researchers was directed toward the pathological-anatomical changes in these organs. However, there are no corresponding reliable indications of such changes to be found in the literature. Since this feature extends to other internal organs as well, it remains to be seen whether the primary disturbances of elementary structure of tissues in man under extremal conditions caused by general cold trauma either do not exist or are such that they cannot be recognized by modern methods of morphological study.

Vishnevskiy's spots are hemorrhages located along the pathways of the blood vessels, very superficial with respect to the mucous membranes of the stomach and easily scraped away with the handle of a scalpel. Their dark color, as suggested by A. V. Orlov, is due to conversion of hemoglobin into hematin as the result of the action of hydrochloric acid in the gastric juice. The mechanism of this conversion, however, is difficult to understand, inasmuch as in the absence of erosion of the mucous membrane of the stomach there is no direct contact between the blood in the extravasates and the hydrochloric acid. Vishnevskiy's spots have not been shown to be pathognomonic for death from general cold trauma, inasmuch as similar changes have been observed when the corpses of starvation victims have been autopsied, or those who have died from poisoning, chronic asphyxia, certain diseases of the brain and various forms of violent and sudden death (V. N. Sheynis, 1943).

The post-mortem (and non-vital) changes in the organs and tissues include freezing of the fluid and blood in the ventricles of the brain and chambers of the heart, as well as freezing of the soft tissues of the extremities and face. Even in artificial freezing of animals or the extremities of a human corpse (for example, the wrists), the latter do not become fragile, but maintain considerable mechanical strength. The freezing of a corpse does not mean that it loses its mechanical strength. Similar false concepts regarding the increased fragility of frozen extremities, the possibility of damaging them or even breaking them off when struck, can be found in old literature on freezing /226 and frostbite.

Heat insulation against low ambient temperatures is critical for human life. Insulation against the pathogenic effect of external cold is achieved

by means of housing, clothing and foot wear. Human life without protection against the cold is theoretically possible only within narrow territorial limits, close to the Equator.

Protection of man against low ambient temperatures is accomplished primarily through mechanical thermoregulation, as well as the phenomenon of acclimatization. Thermoregulation plays an extremely important role in ensuring normal physiological processes. However, its mechanisms are themselves incapable of preventing a drop in tissue temperature. The external temperatures extant on the Earth are such that under ordinary conditions of human vital activity only the prolonged action of external cold governs the development of cold trauma; it is only under conditions of very low temperatures in space, and to a lesser extent near the poles, that it becomes theoretically possible to have instantaneous freezing and frostbite. However, the periods during which general cold trauma develops become relatively short if they are combatted only by mechanisms of physiological thermoregulation. Thus, for example, in shipwrecks that occur during the cold season of the year, exposure of a human being to water at temperatures close to 5-10° for more than 30 minutes always leads to an extremal state and death caused by general cold trauma. Shipwreck victims and those whose clothing has become soaked so that it conducts heat and no longer protects them against the surrounding cold, perish from freezing in a short time. These observations of Grosse-Brockhoff (1954) were supported by G. N. Klintsevich (1970). Following shipwreck, victims were exposed to water whose temperature did not exceed 6° for a maximum of one hour. The victims' clothing varied from light summer clothing to winter clothing. The latter was characterized by considerable thermoprotective properties and a lower tendency to become thoroughly soaked. Several of the victims wore life jackets, which enabled them to stay at the surface of the water even after losing consciousness. Clinical observations of those rescued as well as pathological-anatomical data indicate that persons under such conditions, even during the first few minutes, develop phenomena dangerous to life. A significant percentage of the victims who were in icy water for no more than 40-50 minutes died, although their clothing played an important role in preventing lethal injury. Instant death in icy water was found to be possible.

In other victims, problems with the basic physiological functions developed gradually, particularly inhibition of the activity of the nervous system and circulation. This was due to the high cooling capacity of ice water and the strong stimulatory properties of the latter, which caused loss of consciousness following weakening of the latter within the first 20-40 minutes. Following a brief rise in body temperature, the latter fell once more. It is important that in the case of cooling in water the variations in body temperature are not always significant, since disturbances of respiration and the cardiovascular system rapidly lead to death. Although bradycardia is progressive, death occurs primarily from cessation of respiration. These observations have been confirmed in materials from forensic medical autopsies of shipwreck victims and those who were kept at the surface of the water by their life jackets although their heads were in the water. Pathological-anatomical studies of such victims have not demonstrated that death occurred from drowning. This indicates that respiration stopped before cardiac activity ceased. /227

Among other phenomena associated with general cooling in water, we can mention rapid development of shivering, acute paleness of the cutaneous coverings, rapid development of numbness, and spasms of the extremities. A state of depression and general weakness develops very rapidly, with complete indifference on the part of the individual as to his fate. These phenomena sometimes reach such a degree that persons who are in the water cannot make even the slightest effort to rescue themselves (for example, by grabbing a life preserver thrown to them). At the same time, however, it is difficult to separate them from any floating objects which the victims have used to keep themselves on the surface. It should be pointed out that phenomena which threaten life can develop immediately after removal of the victims from the water. Some of these individuals lose consciousness only aboard the rescue vessel and it has not always been possible to save them in this condition.

As was shown by our experimental observations, infusion of cold blood into the peripheral veins of an animal has no influence on its body temperature to any noticeable degree. Corresponding experimental studies were performed in the laboratory of I. R. Petrov and served as a factor in deciding not to heat preserved blood in hot baths prior to transfusing it. There is reason to believe that the heating of preserved blood which is nowadays carried out universally after this blood has been taken out of the ice box, raising it only to the level of room temperature in the operating room, has prevented many of the negative consequences observed in the past due to overheating of transfused blood in the course of blood transfusion.

We can see from numerous examples in plant and animal life that the lower limit of temperature for life is much less distinct than the upper one. While 55° or a little more is a definite limit for life due to the protein coagulation which takes place at that temperature, low temperatures do not cause protein coagulation even when the latter freezes (P. Yu. Shmidt, 1935). The less complicated the living organism, the higher its resistance to cold. Low negative temperatures, down to -192°, can be withstood by cholera vibrions for periods lasting from 20 hours to 7 days. Worms and snails are very resistant to freezing. In the experiments of L. K. Lozino-Lozinskiy (1943) tissues taken from the brain, lungs and liver of rabbits and dogs were frozen at temperatures of -7 and -5°; after thawing, the assimilation of oxygen and excretion of carbon dioxide in these tissues took place more intensively than it did before they were frozen. Hence, tissues and organs of vertebrates are capable of withstanding total freezing. Under prolonged exposure to cold, freezing of tissues may occur. However, it is immeasurably more important (as experience shows us, especially experience gained in wartime) that the development of negative temperatures in tissues is by no means necessary for the development of cold trauma, particularly the general variety. In addition, it has been found that irreversible changes in the tissues, as well as lethal general hypothermia, even occur under the influence of positive external temperatures, which obviously do not cause freezing but disturb the blood circulation, particularly in the peripheral regions of the human body. If these disturbances last for even a short time, they can cause the onset of local and general cold trauma. Thus, it is not the physical but "biological" zero which determines cold trauma. This term, as used by Ye. V. Maystrakh (1964), was introduced to the literature by Beleradek: biological and not physical zero /228

characterizes the life and activity of man under the specific conditions of its cooling. It is important that biological zero for warm-blooded animals means positive and rather high tissue temperatures (25-30° or more). As we know, the temperature of the human body in the course of its vital activity varies within narrow limits of 1° (36-37°) and any significant or prolonged drop causes general cold trauma.

The basic effect of cold on the tissues consists in a change in the tissue colloid state. In addition, a change in the solubility of the non-colloid substances is involved, with a decreased rate of chemical processes, changes in chemical balance and so forth. All of these processes form complicated combinations with inflamatory phenomena and create a pathogenesis of freezing which is highly complicated. However, the primary phenomena in the tissues can be explained by the laws of colloid chemistry. Normal vital activity of the cell is impossible without normal colloid conditions. Excessive disturbances only temporarily interrupt the normal life of the cell. However, if the protoplasm loses its ability to recover fully, the cell will be permanently damaged. It is impossible to see these changes under the optical microscope and it is only in ultramicroscopic research that the decrease in the dispersity of the protein and the approach of the colloid system to the cooled state can be seen. It is necessary in this regard to emphasize that the time factor of the action of the cold is considered critical to the development of irreversible changes, inasmuch as it is only as the result of the prolonged action of moderately low tissue temperatures that a transition of the tissue protoplasm hydrosol into hydrogel takes place.

There is no doubt that the individual primary colloid-chemical conversions cannot explain all of the complicated pathogenesis of freezing. Burton and Edholm (1955) feel that death under hypothermal conditions is instead a result of the disruption of coordination and integration as a whole. Special emphasis should be placed on the fact that all homoiothermal as well as certain poikilothermal animals die long before the protoplasm in their cells freezes. Ye. V. Maystrakh (1964) points out some specific features of so-called cold shock, particularly the lack of coordination of the vital functions which negates the direct analogies which have been made between traumatic and cold shock. The term "shock" is very approximate as it applies to the latter state.

The prolonged action of low ambient temperatures under certain conditions can cause tissue temperature at the periphery of the body in man and warm-blooded animals to drop gradually. After reaching a certain level, the temperature decrease accelerates, since the biological thermoregulatory mechanisms cease operating at this time (circulation, metabolism) and only the physical thermoregulatory mechanisms continue functioning; the most important of the latter is the low thermal conductivity of the skin and subcutaneous cell structure. Hence, the skin acts as a protective and vulnerable organ in cold trauma. In these functions it is closely linked to the internal organs through the nervous system and the blood and lymph vessels.

The significant participation of the blood in the pathogenesis of cold trauma is governed primarily by the systematic transport of heat to the cooled peripheral portions of the body. However, authors are not prone to

overestimating the significance of this fact, since in their opinion the spasms of the vascular network practically lead to a complete exsanguination of the cooled extremity at a certain stage of development of freezing. Nevertheless, /229 there is no doubt that during the stage which precedes vascular spasm the blood plays an important role in the process of physical thermoregulation. Moreover, the increase in erythrocyte volume under the influence of cold (experiments of V. A. Manasein) and the stronger chemical bonds between hemoglobin and oxygen which develop under low temperature conditions characterize the significance of the blood in tissue gas exchange during freezing, and consequently in its pathogenesis. Under extremal conditions, caused by general cold trauma, there are no changes in the osmotic resistance of the erythrocytes (T. Ya. Ar'yev, N. A. Esberg, 1937). Consequently, the polyglobulia which is characteristic of a cold extremal state is due not to hemolysis but to a relative increase in red blood cells in the peripheral blood.

In the general and local action of cold, leukocytosis is observed in the peripheral blood in addition to pseudoeosinophilesis. The results of our experiments on animals have proven to be somewhat contradictory, as have the data in the literature concerning the changes in the sedimentation rate and coagulation of the blood. Data on the stronger links between oxygen and hemoglobin in general cold trauma are of great interest. The studies of K. M. Bykov and his associates demonstrated that in animals the blood coming from frozen extremities undergoes a gradual increase in oxygen content. A sharply manifested smoothing of the arteriovenous oxygen and carbon dioxide differences takes place. In other words, regardless of the treatment of these facts, it remains obvious that there is a serious oxygen starvation in the cooled tissues, which serves as a cause of subsequent pathological processes.

In the course of general cold trauma following irregular initial acceleration of respiration, the latter gradually slows down and grows weaker, circulation is disrupted and (in deep cooling) fibrillation of the heart is probable (V. A. Bukov et al., 1964). In all forms of cooling, including cooling of an isolated organ, the heart reacts by progressive slowing of the rhythm of the contractions. Revival of rabbits even after breathing and heart beat have stopped, if carried out immediately afterward, frequently achieves its purpose but only at forced rates. Hence, cessation of cardiac and pulmonary activity during general cooling of animals is theoretically reversible. This means that it is theoretically possible to revive persons who have frozen.

The symmetry of the injury is indicative of the involvement of the sympathetic nervous system in cold trauma pathogenesis. A characteristic feature of freezing is increased tone of the sympathetic nervous system, due to hyperfunctioning of the adrenals. A generality of the phenomena can be seen, which occurs under the influence of cold upon the organism and with stimulation of the sympathetic nervous system, caused by injection of adrenaline. Obviously the process involves other sections of the endocrine system. In particular, the thyroid gland is involved in the thermoregulation of the organism in warm-blooded animals.

The considerable importance which was placed on the vascular reaction in freezing by M. Ye. Marshak (1965) provided him with a basis for distinguishing between "true gangrene from frostbite" accompanied by freezing of the tissues and "ischemic gangrene" in which primary cellular necrosis is absent and death of the tissues is caused by their starvation due to vascular spasm.

The degree of decreased blood flow as a function of cooling intensity is expressed by the following figures (after V. N. Chernigovskiy and N. I. Kurbatova, 1941). /230

During Cooling:		During Heating:	
Temperature	% Relative Blood Flow	Temperature	% Residual Blood Flow
32°	100	12.5°	20
23°	50	16°	30
19°	30	18.5°	50
11°	15	23.5°	100

From these figures we can draw two conclusions which are important for an understanding of the pathogenesis of the general cooling of warm-blooded animals: 1) a significant (up to 50%) restriction of blood flow, i.e., a severe disturbance of circulation, which takes place even at a comparatively high body temperature in the homoiothermal animals (23°); 2) recovery of circulation in the course of heating takes place at a lower temperature than its cessation in the cooling process. The first of these conclusions explains the serious cases of freezing that are seen in the clinic (so-called trench foot) as well as freezing under the influence of comparatively moderate but long-acting low ambient temperatures. The second conclusion is responsible for the considerable reversibility of pathological processes seen in the clinic in cases of general and local cold trauma.

In olden times (and even today) tissue changes during freezing have continued to be explained by a narrowing of the lumina of the blood vessels, caused by thrombi as well as spasm. Thrombi are in fact observed in extremities which are amputated because of frostbite and in experimental production of frostbite in animals.

General disturbances of circulation in cold trauma in warm-blooded animals are the consequence of suppression of function of the respiratory center of the brain by cold. At the same time, the vasoconstrictive center of the medulla oblongata ceases its activity (V. A. Bukov, 1964). The heart, however, is relatively tolerant to cooling and ceases its contraction even outside the organism only at a relatively low temperature such as 9-10°. Moreover, ventricular fibrillation, which occurs in an extremal state caused by cold trauma, in some cases may disappear spontaneously, i.e., it is a reversible phenomenon that disappears as the tone of the blood vessels returns under the influence of heating the heart (V. A. Bukov, Yu. Yu. Yegorov, 1964).

Several authors consider cold to be one of the basic etiological factors in the pathogenesis of many forms of obliterative endarteritis, inasmuch as the

regressive phenomena in the cells, caused by cold, lead to the formation of subintimal edema and therefore hypertrophy and swelling of the supporting tissues.

In studying the problem of freezing, researchers have come across a considerable degree of complexity in its etiology. Such factors as increased humidity and compression of the vessels are incapable of causing the freezing syndrome, and their role is restricted simply to creating conditions for the action of low temperature. The critical factor is tissue hypothermia.

There are a number of biological characteristics of the effect of cold upon man; first among these is the inverse relationship observed between the degree of tolerance of an organism with respect to cold and the complexity of its structure. The more complexly structured the organism, the more sensitive /231
it is to the effect of low temperatures. Thus, the protozoa, to which the concepts of "frostbite" and "freezing" apply not only relatively but absolutely, possess a high degree of resistance to cold. The organisms of higher animals are capable of withstanding considerable local supercooling at temperatures which would unavoidably lead to death in the case of general cooling.

Characteristics of the Action of Low Temperatures

Death of tissues from freezing is regularly limited to the joints composing the leg and foot and the hand and arm, and in extremely rare cases can spread proximally but never cross the boundaries of the knee and elbow joint. This is probably because such a spread is objectively prevented by the lethal general hypothermia that unavoidably accompanies extremal conditions.

The second biological characteristic of low temperatures that governs the onset of frostbite to a large degree is the incomparably greater resistance of tissues, cells and living protein in general with respect to cold than to heating. High cold resistance is the reason why a specific and rather significant length of exposure to low temperature is required to cause pathological processes. In other words, the time factor is critical in the majority of cases for the development of irreversible tissue changes. It is well known that the brief action of even very low temperatures takes place without a trace or damages the tissues to a very slight extent. Thus, according to the experience of N. I. Gerasimenko (1950), amputation of the extremities, carried out under local anesthetic by cooling the tissues in the area of the cut to 5-10° for 2-3 hours, is not accompanied by subsequent death of the tissues; instead, the wound on the stump healed with primary tension.

We know from the experiments of V. N. Chernigovskiy and I. I. Kurbatova that cooling one extremity of an animal causes ischemia of the other. This repercussion has a complex reflex mechanism and must be taken into account when studying the pathogenesis and clinical aspects of local cold trauma. In the experiments of M. Ye. Marshak, a bandage moistened with ice water was applied for 10-15 minutes to a shaved area on the skin of a rabbit (12 × 15 cm), after which the body temperature of the animal rose 1°. These results show the sensitivity of the mechanism of thermoregulation in homoiothermal animals.

Cooling isolated tissues of homoiothermal creatures initially not only fails to inhibit (but even increases) cellular respiration (L. K. Lozino-Lozinskiy, 1963).

The pathogenesis and clinical pathology of general and local cold trauma differ in other ways than the period of development. Thus, the more serious form of frostbite (so-called trench foot), in contrast to freezing, takes place with symptoms of secondary death of tissues and general infection. This pathogenesis is not characteristic of freezing. Accordingly, a distinction must be made between the principles of recovery from an extremal state with local and general cold trauma.

The third biological characteristic of the effect of low temperatures on man is a slowing of the biochemical processes, directly proportional to the decrease in tissue temperature. This relationship also applies to biological processes. Tissue growth is slowed down by cold, and fluid intake slows down as well; the inflammatory process proceeds sluggishly, and there is an inhibition of embryonal development. The processes of vital activity in animals slow down in response to cold. The classical example of this slowdown is hibernation, particularly hibernation (anabiosis) in animals during which there is no tissue damage like that which occurs when isolated tissues are stored in ice. The injury and destruction of tissues in animals and man occurs only if there is a prolonged decrease in tissue temperature and a related slowdown of the processes of vital activity in some area at the periphery of the body, while all the other organs and tissues retain their normal temperature and normal metabolic intensity. Between the tissues in the peripheral areas, cooled down to limits incompatible with the existence of processes of vital activity, and the tissues of the central areas there is a transitional point where the temperature is low enough to slow down the vital activity of the cells sharply, yet is below body temperature. This range is the future zone of demarcation and accordingly marks the gradual drop of tissue temperature with approach to the peripheral cooled area; degenerative and necrotic processes develop in the future demarcation band, approaching continuous necrosis. /232

Hence, the life of nonisolated tissues and cells with prolonged local cooling is impossible under conditions of continuing vital activity of the rest of the organism. The reason for this view consists in the fact that because of tissue hypothermia the links are broken between the centers of the vital activity of the organism. Consequently, the uncoordinated vital processes are distorted to a greater degree in the peripheral areas, eventually leading to death of the cells and tissues.

The processes of cellular degeneration and necrosis which occur during freezing at the more distal lines of demarcation is influenced by a weakening of the immune mechanisms in the cooled animal. The mechanism of developing infection evidently involves (to a large degree) the fact that reactive inflammation is sharply restricted under low tissue temperature conditions; this promotes greater intensity of suppuration. The importance of suppuration for prognosis of frostbite can be judged from the fact that purulent frostbite usually takes place under very favorable conditions, because any extensive

freezing that occurs, particularly in war time, rarely occurs under aseptic conditions.

The cells and tissues that have perished as a result of prolonged exposure to cold show no symptoms of death before they are heated which could be recognized by modern histological, histochemical or other methods.

The morphological symptoms which are specific to freezing are not observed when frozen human cadavers are autopsied (A. K. Smyslova, 1909). The processes associated with low-temperature effects begins to develop only when the tissues of cold-trauma victims are warmed. These changes consist in the death of tissues in which low temperature has produced total and irreversible cessation of the vital activity of the cells: degeneration in those areas where damage to tissues was completely or partially reversible, and inflammation in zones that border the necrosis and degeneration. In many cases of frostbite it is impossible to evaluate its degree during the first few hours and even days following warming of the victims, since by no means all of the injuries which occur in the course of local cold trauma become manifest within 2 or 3 weeks following heating. The latent nature of tissue damage occurring during the initial period of cold trauma, i.e., prior to warming victims, constitutes the fourth biological characteristic of frostbite, distinguishing this trauma from all other forms of trauma in man and animals. The cold, so to speak, preserves the tissues for the entire period that it is active, but the longer this "preservation" lasts, the more serious its consequences, as determined following cessation of the action of cold. Direct measurements of tissue temperature conducted in a clinic by S. S. Girgolav are of great importance in clarifying the nature of the so-called latent period of cold trauma described above. /233

The skin, its nerve mechanisms and the network of blood vessels are the first to be affected by cold trauma. The same is true to a lesser degree of the air passages in the lungs. Experience with living and working under Arctic and Antarctic conditions indicates that even a comparatively brief inspiration of cold air can cause direct and serious cold trauma to the lungs, frequently leading to extremal conditions (see Chapter 11).

Cold trauma arises as a result of action of external low temperature and a number of corresponding factors. If this effect is brief, some and frequently all the pathological processes are reversible. The reversibility of the tissue processes frequently observed in experimental conditions and in the clinic in cases of cold trauma are very clearly manifested and constitute the fifth biological feature of the effect of low temperatures on the living organism.

General Cold Trauma

Cases of general pathogenic effects of low temperatures on the human organism are most frequently encountered in areas with a cold climate, i.e., primarily in Northern regions. However, extremal states in general cold trauma, although they are observed primarily in Northern regions, have also been recorded even in the Crimea, the Caucasus and Northern Asia. More than

one-third of all the cases of general cold trauma occur during autumn and spring. This is explained by the fact that the pathogenic effect of relatively low ambient temperature is considerably amplified during periods of increased atmospheric humidity and wind which disturb the mechanisms of artificial and natural thermoregulation. Many researchers have firmly established the extremely unfavorable role of alcoholic intoxication. It occupies first place among the factors which promote the development of cold trauma (67%), followed immediately by exhaustion.

The extremal state in general cold trauma is characterized by an unconscious state, very weak pulse, bradycardia, and infrequent respiration. Rigidity of the extremities and their flexile contractures, particularly the lower jaw, are characteristic.

A. V. Orlov (1946) was by no means the only one in the world literature to collect and generalize a great many clinical observations of general cold trauma. The author sees it as a physiological phase with phenomena of irritation of the sympathetic nervous system and neuroendocrine modification. The direct effect of cooled blood on the corresponding nerve centers can be excluded, as well as the nerve endings in the smooth muscle of the walls of the blood vessels. Maintenance of constant body temperature in the physiological phase of general cooling in man is the result on the one hand of a /234
decrease in heat loss to the environment and on the other hand of an increase in heat production through intensification of biochemical processes. The increase in muscle tone and reflex stimulation, as well as in the oxidative processes in the internal organs, particularly the liver, are aimed at the compensatory increase of heat formation. This is promoted by carbohydrate mobilization from the glycogen deposits in the liver and muscles (T. A. Achkasova, 1953) as well as by stimulation of the functions of the sympathetic nervous system. All these natural thermoregulatory mechanisms are capable (albeit to a very slight extent and for a short period of time) of preventing the second phase of general hypothermia, i.e., general cold trauma and its extremal states.

The clinical picture of general cold trauma has been described on many occasions, but its clinical-pathophysiological classification, which is described briefly below, was worked out by A. V. Orlov (1946).

Convulsive stages. Loss of consciousness. The cutaneous coverings are pale, slightly cyanotic on the exposed portions of the body, and cold to the touch. The muscles are tensed. Trismus is particularly evident (convulsive tonic contraction of the masticatory muscles). The upper extremities are in a state of convulsive flexural contraction. The lower extremities are bent half-way, more rarely extended. In serious cases, the muscles of the abdominal press are tensed. The testicles are drawn up and the scrotum contracted. Respiration may be shallow, sometimes irregular. The pulse is weak and irregular, in some cases arrhythmic and difficult to perceive. The pupils are contracted, do not react to light, or have a sluggish reaction to it. The eyeballs are rolled back. The eyelids are usually not completely closed. Soon after the patient is brought into a warm place, repeated involuntary urination or total incontinence of urine is observed.

In the freezing stage, the body temperature was found to be 26-30° (A. V. Orlov). It must be emphasized once more that the failure of general practice to use thermometers whose scales cover a temperature range from 35-15° (i.e., temperatures at which human life is theoretically possible) must be viewed as the most probable cause of extremely late diagnosis of freezing or failure to recognize it at all. The maximum blood pressure in the convulsive stage of freezing is usually low (up to 95 mm) and the minimum remains normal or even slightly increased.

A. V. Orlov emphasized that the clinical picture described above does not prevent a lethal outcome by virtue of the high potential reversibility of the freezing. This is also indicated by the observations of the revival of a 17-year old girl who was buried in snow for 51 days.

The convulsive stage of general cooling. The clinical symptoms of this milder stage of freezing consist in pronounced somnolence, loss of consciousness, disturbance of speech (bradyphasia, disarthria), absence of mimics. According to the data of Burton and Edholm (1955), even a slight decrease in brain temperature (for example, in artificial hypothermia) causes pronounced disturbances of mental capacity. The body temperature in the stupor stage varies from 29 to 32°; the pulse frequency is 28 to 52 beats per minute. Arrhythmia is rare. The arterial pressure level is the same as in the convulsive stage. There are usually no profound respiratory disturbances.

Adynamic stage of general cooling. In this stage, consciousness is retained for the most part, or merely impaired. The patients are somnolent and /235
complain of weakness, fatigue, dizziness, sometimes headache. Their speech is disjointed and slow, but quiet and relaxed. The patient may sometimes come in for treatment, supported under the arms. The body temperature varies from 30-32°. Those who have withstood freezing state that at the beginning of supercooling, before they lost consciousness, they felt warm; it seemed to them that they were sitting on a hot stove, together with their parents, and they felt happy and cheerful (A. V. Orlov, 1946).

Heating and the Consequences of Cold Trauma

Persons with frostbite must be heated in a bath in which the water temperature is gradually raised to 40°. A. V. Orlov emphasized that placement in the bath and absence of other first aid measures in cases of freezing can last up to 7 hours and still give a positive result. The body of the frozen person must be submerged completely in the bath, seeing only that he does not drown. Before being put in the bath, the victim is given a subcutaneous injection of caffeine or camphor oil solution. He is given hot tea to drink if he can swallow it, as well as hot food; he is then given 20-60 ml of 40% warm glucose intravenously. In the bath, the victim's body is massaged, using soapy washcloths. The victim stays in the bath, as a rule, from 15-20 minutes to 1 hour, after which he is wiped dry and placed in a warm bed. Further treatment is of a symptomatic nature.

V. N. Chernigovskiy and I. I. Kurbatova (1953) established experimentally that rapid warming of supercooled animals promotes earlier recovery of blood flow and subsequent restoration of initial tissue temperature. The favorable effect of rapid heating of animals subjected to cold trauma has been clearly illustrated in other experiments (P. N. Veselkin, 1943; L. N. Komarova, 1949; T. A. Achkasova, 1953).

Experience in treating cold trauma during World War II conclusively overturned the false theory of slow and gradual heating of those suffering from cold trauma. In his monograph, A. V. Orlov wrote that the old method of slow heating of freezing victims "must be once and for all forgotten" and that "rapid heating must be used without exception" and that "only this will ensure prevention of further heat loss in the freezing victim".

During the recovery period, victims of general cold trauma experience problems in swallowing and later develop numerous complications, particularly various disturbances of the nervous and cardiovascular systems, pneumonia, disturbances of gastric function and of other internal organs, attacks of chronic colitis and pulmonary tuberculosis (N. I. Gerasimenko, 1950 and others). The clinical observations of A. V. Orlov agree with the experimental research of N. D. Dmitriyeva (1964), indicating that animals that have been brought out of rigid hypothermia show numerous motor and trophic problems for a long time, as well as anemia and other pathological changes in the blood composition. These data indicate that after surviving general cold trauma the victim can develop chronic and persistent clinical syndromes which N. D. Dmitriyeva, following the theories of S. S. Girgolav, has referred to as "cold disease".

According to the data of A. V. Orlov, 19% of all cases of general cold trauma are accompanied by mild frostbite. This fact, very important in the pathogenesis of cold trauma, is supported by the practical treatment of cases /236
of general cold trauma during peacetime and most noticeably under military conditions. It is obvious that the extremal state in general cold trauma is formed in much shorter times than in local, even serious, frostbite.

Conclusions

The extremal states caused by cold trauma are produced by a decrease in body temperature in man and animals to a level at which the natural homoiothermal state is replaced by poikilothermia. The development of the latter takes place not only at negative ambient temperatures but even at positive ones, if the exposure is a long one. This means that cold trauma is theoretically possible when the temperature falls below 37°. However, this critical temperature is much lower in practice.

In order for extremal states related to cold trauma to arise, it is often necessary to have a disruption of the artificial thermoregulatory system of man (housing, clothing and footwear). After loss of the protective effects of the latter, even for a short time, extremal states do not occur as the result of the action of natural thermoregulatory mechanisms. Hence, for effective

treatment of cold trauma, it is necessary to have four factors acting jointly. The first of these is low ambient temperature, the second is optimum duration of its action, the third is disruption of the artificial thermoregulatory system, the fourth is disruption of natural thermoregulation. However, the primary factor in the development of cold trauma in man is the disruption of artificial thermoregulation, since man can live even under outer-space temperature conditions when it is retained.

The significance of the pathological state in cold trauma consists in the disturbance (dyscoordination) of the vital activity of physiological systems and organs in man, caused by interference with the blood circulation. The primary cause of the latter is the disruption of circulation in the brain, which regulates functional and vital activities in man. The triggering mechanism of the disturbances which develop is the steady decline in the internal body temperature to the level of so-called biological zero, whose range is difficult to determine precisely inasmuch as it has wide limits, from 30° to 22°. Further cooling leads to the onset of lethal hypothermia. In theory it is important that the extreme states involved in cold trauma and the death to which it leads occur without freezing of the tissues; hence it is only the corpse which freezes. The initial stages of general hypothermia are reversible if the universal disturbances in circulation are relatively brief and on a small scale. Local cold trauma with death of frozen extremities, if it develops in conjunction with general cooling, has a particularly serious course and causes a very high probability of extreme states. This seriousness is also dependent upon sepsis and septicemia, which are particularly frequent in so-called trench foot -- serious bilateral gangrene of the lower extremities. First aid in cold trauma consists of raising the body temperature to normal as quickly as possible. Inasmuch as body temperature in frozen individuals who are still alive cannot be less than 26°, the temperature of the bath in which they are heated also must be below this level. Old methods of treatment in which the victims of freezing were rubbed with snow in the cold, without bringing them into a warm place, were based on the false assumption of the pathogenesis of freezing and frostbite as a freezing of the tissues and cells. Extreme states caused by septic complications of serious frostbite are treated by radical methods of modern surgery. /237

The prevention of general and local cold trauma, as well as extremal states in them, is theoretically carried out by a system of modern hygiene involving housing, clothing and boots.

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HYPOTHERMIA

Professor B. A. Saakov

The first detailed studies of the effects of cold on the organism were /237
conducted by the famous Russian anatomist and physiologist A. P. Val'ter in 1863. By cooling rabbits down to a body temperature of 20°, Val'ter described the pattern of the hypothermia which developed and suggested the possibility /238
that "very fine and delicate operations contraindicating the use of other anesthetics" could be carried out in this condition. The results of these studies were expanded upon in other basic research efforts (Ya. I. Yakobiy, 1864; I. R. Tarkhanov, 1871; A. Khorvat, 1876; F. F. Lapchinskiy, 1880).

Some very interesting studies, with highly promising results that were considered fantastic up to that time, were carried out by P. A. Bakhmet'yev, who wrote a text book on anabiosis (1902, 1912 a, b, c). Encouraged by the results of his work, the author suggested the possibility of producing anabiosis in warm-blooded animals. In the work of his successors, equally interesting trends developed and the conclusions drawn by Bakhmet'yev were expanded further (I. I. Murygin, 1937; G. A. Mashtaler, 1941; N. N. Sirotinin, 1938-1964; N. I. Kalabukhov, 1946; E. Ya. Grayevskiy, 1948; P. Yu. Shmidt, 1948; L. K. Lozino-Lozinskiy, 1952; A. D. Slonim, 1952; Ye. V. Maystrakh, 1950-1964; P. M. Starkov, 1957).

In clinical practice, several forms of the harmful effects of cold are encountered. This consists in particular of frostbite, i.e., varying degrees of injury to the peripheral parts of the body.

The question of the general effect of low temperature is an important one for the theoretical and particularly the practical aspect of medicine. The general cooling or freezing that develops under these conditions arises in conjunction with sublethal or lethal hypothermia. In clinical practice we quite frequently encounter cases of general cooling, indicating the high level of timeliness of research devoted to the pathogenesis of hypothermia. It may confidently be stated that there has never been a war extending through the cold season of the year which did not involve enormous losses from freezing and frostbite.

The question of the temperature boundaries of hypothermia is also of great interest. It has been determined that the average minimum temperature of the body which can be withstood by the organism is 0-5° for the marmot, 13-15° for the rat, 14-16° for the cat, 18-20° for the dog and 24-26° for man (Crismon, Elliott, 1947; Burton, Edholm, 1955).

Under conditions of deep hypothermia, the primary cause of death is cessation of respiration, which arises as the result of inhibition of the respiratory center due to its comparatively high sensitivity to cold (A. P. Val'ter, 1863; A. Khorvat, 1876; V. N. Sheynis, 1943; A. L. Izbinskiy, 1953; P. M. Starkov, 1957; Spurr, 1954; Bartlett, 1955; Kayser, Richert, 1958). On

this basis, the cooling of animals using artificial respiration can be used to produce a greater degree of hypothermia (A. Khorvat, 1876; Ariel, 1943, 1945 et al.).

One of the most dangerous complications in hypothermia is the disruption of cardiac activity, with disturbances of heart rhythm, ventricular fibrillation, and paralysis of the heart. It is considered that the disturbances to cardiac activity can be explained by the direct inhibiting action of cold upon the heart (Crisman, 1944; S. S. Khalatov, 1946). It is more likely, however, that they are the result of secondary influences on the heart, including in particular a hypercapnia which develops, a shift in the acid-alkaline balance of the blood toward the acid side with a deepening of hypothermia (Swan, 1955; Delorme, 1955; Oyama, 1955). The development and severity of the complications is largely dependent on the rate of development of acidosis, rather than on its degree. The decrease in the excitability of the heart muscle as a result of hypokaliemia and hypoxia of the myocardium are of great importance.

In a number of instances, due to the use of additional methodological /239
approaches, it is possible to achieve a significant degree of cooling of the organism with subsequent recovery of functions. The use of artificial respiration alone makes it possible to cool down anesthetized rabbits to the 17-10° level (Ariel, 1943) and dogs down to 17-11° (Haterius, Maison, 1948). Under conditions of hypercapnic anoxia, rats and mice can be cooled down to 0-1° with total cessation of respiration at 9° and stoppage of the heart at 6° for 60 to 75 minutes. Following reheating by means of microwave diathermy or incandescent lamps, it was possible to revive 80-100% of these animals successfully (Andjus, 1955; Andjus, Lovelock, 1955; Lewis, 1957; J. A. Miller, F. S. Miller, 1959). A still greater degree of cooling can be achieved by using extracorporal circulation of the blood. In particular, the temperature of anesthetized dogs can be brought down to 8°, recorded at the mucous membranes of the throat (Drew, 1959) and even brought down to a rectal temperature of 0° by means of a pump oxygenator (Gollan et al., 1954). By changing the reactivity with respect to the harmful action of cold as a function of age, Ye. M. Prokop'yeva (1953) found that young homothermal animals have far greater tolerance to supercooling than adult animals. The death of the latter occurs at body temperatures of 18-20°, while it is observed in puppies at 0-10 or 11°. In puppies, death occurred in 50% of the cases from stoppage of the heart, while in adult dogs it was the result of cessation of respiration. Many papers can be found which support the basic conclusions of Prokop'yeva (Churchill-Davidson, McMillan, Melrose, and Lynn, 1953; Gelineo, 1954; Maguire, Merending, 1955, and others).

The harmful effects of cold, causing the extreme state, termed hypothermia, like any other stressor influence, in addition to the syndrome specific to hypothermia, is accompanied by a number of stereotypical reactions, of which the most important is that of the glucocorticoid hormones (L. Ya. Danilova, 1967). However, supercooling, to a greater degree than other extremal influences, is capable of producing pathological changes associated with the inadequate reaction of the hypophyseal-adrenocortical system (Ingle et al., 1957). P. D. Gorizontov and T. N. Protasova (1968) suggest that it is

precisely these characteristics of hypothermia as a stress factor which may form the basis of the pathology of the kidney vessels and those of the heart to a lesser extent.

It is necessary to emphasize that the mechanism associated with the development and production of various forms of reactions to hypothermia is unclear in many respects. This problem is further complicated by the fact that the pathogenesis of hypothermia, as it is encountered under natural conditions, differs markedly from the pathogenesis of artificial hypothermia, and even more so from deep anesthesia.

Principal Pathogenetic Mechanisms of Hypothermia

Neuro-endocrine regulation. Hypothermia reflects a disruption of the balance between the processes of heat formation and heat loss. The nervous system function of controlling and coordinating these processes is disturbed in the very first stages of general cooling. As far back as 1881, V. V. Pashutin indicated the involvement of the nervous system in the harmful effects of cooling on the organism. S. S. Girgolav (1939) felt that the decrease in the temperature of the central nervous system is particularly harmful within the general picture of the action of cold, i.e., the cooling of the brain and spinal cord. The large number of cases of acute hypothermia among human beings was observed by A. V. Orlov as discussed in the previous section. /24
The author concluded that the principal role in the pathogenesis of general cooling should be assigned to disturbances of the higher coordinating vegetative centers. The clinical manifestations of general supercooling include muscular rigidity, clouding of consciousness (G. P. Shul'tsev, 1945), development of the neurites, and loss of sensitivity (A. V. Orlov, 1949). At body temperatures of 29.4 to 26.7°, human beings lost consciousness and the majority of reflexes were inhibited (Collins, Granatelli, 1955; I. A. Piontkovskiy, 1958).

The problem of the changes in the excitability of the nervous system during hypothermia has been of interest to experimenters for a long time. Even I. R. Tarkhanov back in 1871, who cooled frogs with ice, observed the rise in the excitability of the spinal column which he explained as a change in the conditions by which blood flows to the nerve centers. A similar increase in reflex excitability in rabbits and frogs was described by N. I. Levitin (1937).

Cooling of an extremity causes a change in the chronaxia of the muscles on the cooled and intact sides (Bourginion, 1923; Chauchard, Chauchard and Denisoff, 1933). L. I. Ardashnikova (1935), I. M. Vul and Yu. M. Uflyand (1937) found that general cooling causes a shortening of the motor and a lengthening of the sensory chronaxia, times which depend upon the magnitude of the heat loss. The rheobase and chronaxia of the motor centers of the spinal column initially decrease, but at the end of hypothermia they are strikingly lengthened (O. A. Karpovich, 1950). Studying the influence of cooling on non-conditioned salivary reflexes in man, A. A. Dorodnitsina (1937) observed that cooling increases the secretion of the salivary glands. However, all of these data provide only an indirect indication of the changes which occur in the central nervous system.

We must devote more attention to those experiments which showed that the isolated cooling of the brain (accomplished by cooling the blood in the carotid arteries or by other methods) is accompanied by a number of symptoms which are characteristic of hypothermal states in warm-blooded animals (Trendelenburg, 1910; Ye. I. Sinel'nikov and G. P. Gugel'-Morozova, 1934).

The data on the influence of cooling on the function of the vegetative and peripheral nervous systems are equally important. In 1963, A. P. Val'ter was the first to direct attention to the anesthetizing influence of cooling. V. Ye. Delov and Ye. G. Petrova (1946) found that when the tissue temperature drops to 22°, the excitability and conductivity of the sciatic nerve drops very insignificantly, while myoneural transmission undergoes marked changes. Raso (1939) confirms the high degree of sensitivity of sympathectomized animals to cold. P. M. Starkov (1947) reports an increase in the parameters of a number of vegetative functions during the initial stage of hypothermia and the inhibition of these processes with progressive cooling. In studying the influence of hypothermia on the state of interoreceptive reflexes it was found that supercooling a cat considerably reduces (and at the state of deep hypothermia, fully inhibits) the interoreceptive reflexes (T. V. Popova, 1949).

Modern concepts regarding the mechanism of heat regulation are based on the humoral and neural reflex factors involved in it (I. S. Vaynberg, 1946). However, the nature of these mechanisms was determined by a study of the heat receptor functions of the skin and mucous membranes, while comparatively little attention was devoted to the sensitivity of the receptors of the vascular system, particularly the basic reflexogenic zones, to the temperature variations.

In the studies of B. A. Sazkov and K. M. Mokhin (1949, 1950) concerning the condition of vascular reflexes during hypothermia it was found that during /24
initial cooling of an animal reflexes from chemo- and baroreceptors of the carotid sinus increase. Further cooling of the body to 22-25° leads to pronounced inhibition of the reflexes from the receptors of the carotid reflexogenic zone. In subsequent experiments performed on cats and dogs, it was found that the greatest changes involved in hypothermia are seen in the central apparatus of the reflex arc under study (B. A. Saakov, 1952, 1953, 1957; I. D. Boyenko, 1950; Z. P. Yunusova and A. N. Kishkovskiy, 1951; Dubecz, Kertal, Koka and Lunday, 1955; Donnet, Zwirn and Ardisson, 1955; Malmejac, Neverre, Plane, Montero and Malmejac, 1956). The magnitude of the chronaxia of the nerve centers increased with the degree of cooling of the body and reached a maximum with a drop in rectal temperature to 28-29°.

The results of experiments aimed at studying the influence of cooling on the function of the vegetative nerves are highly contradictory. According to the data of A. N. Khorvat (1876), A. S. Ignatovskiy (1901), and A. Zubchenko (1903), inhibition of the excitability of the vagus nerve was observed when the animal's body was cooled to 21-22°.

This same phenomenon was observed in the experiments of Raso (1936) at a much lower temperature. A. I. Yakobiy (1864) observed a dilation of the pupils in rabbits that were in a state of lethal hypothermia, and ascribed this to a

heightened sympathetic nerve function. Raso (1936) on the other hand pointed out the total inhibition of the sympathetic system at a body temperature of 26° in the rabbit.

P. M. Starkov, P. G. Zherebchenko, N. V. Klykov, and O. A. Karpovich (1955) found that the most significant and earliest changes in the hypothermia occur in the higher sections of the central nervous system, particularly in the cerebral cortex. Conditioned motor reflexes in the dog disappeared completely at body temperatures of 27-30°. L. V. Komarov (1955) found that when the body temperature falls by 2-3° there are no changes in the motor-defensive and conditioned respiratory reflexes. During hypothermia (28°) there is a slight increase in the tone of the cerebral cortex, followed by gradual extinction of the conditioned reflexes until they disappear altogether. Conditioned respiratory reflexes disappeared more rapidly than motor types. Inhibition and disappearance of the spastic reaction in response to electrical stimulation of the cerebral cortex occurred at hypothermia below 25°, while direct stimulation of the central motor analyzer in the cerebral cortex caused movement of the paws even at a body temperature of 20°.

Data on the changes in the excitability of the sympathetic and parasympathetic nervous system, as well as the spinal cord, can be found in the works of A. G. Bukhtiyarov (1948, 1955), Koella and Ballin (1954), Gellhorn (1955), Koizumi, Malcolm, and Brooks (1954), and Brooks, Koizumi, and Malcolm (1955). A. G. Bukhtiyarov, working with deep supercooling, observed a decrease of pressor response to adrenaline and lobeline. In studying the excitability of the vegetative nervous system in the dynamics of hypothermia, Koella and Ballin (1954), as we ourselves did earlier, observed clearly pronounced periodicity. With a decrease in body temperature to 31-33° there was an increase in the pressor reaction of the blood pressure to electrical stimulation of the posterior hypothalamus and injection of adrenaline. When the body temperature fell to 25-29°, the pressor reactions decreased significantly. At low temperature there was a significant lengthening of the hypotensive e effect of mecholin, acetylcholine and histamine. Injections of adrenaline or noradrenaline under conditions of hypothermia caused reduced pressor responses involving the blood pressure. According to the data of Gellhorn (1955), the reactions which occurred in response to the direct stimulation of the hypothalamic region by the square-wave pulses of current at lowered body temperature were found to be reduced. /242

During the initial period of hypothermia, the reflex activity of the spinal cord is slightly increased (Barron and Mattews, 1938; Grundfest, 1941; Ye. A. Zherbin, 1950; Koizumi et al., 1954). Some authors feel that it is caused by improved synchronization of the stimulation rather than increased stimulability of the spinal cord (Pinelli, Buchthal, 1953). Where the excitability of the spinal cord is concerned, Kouzumi, Malcolm, and Brooks (1954) observed periodicity in its changes in the dynamics of hypothermia. In 1950, in studying the electrical excitability of the saphenus nerve, B. A. Saakov and K. M. Mokhin found that during the initial period of hypothermia (1-3° drop in body temperature) there is an increase in the excitability of the spinal cord. More pronounced hypothermia is accompanied by a decrease in its excitability. Brooks, Koizumi, and Malcolm (1955) studied the reaction of the

anterior and posterior spinal roots in decerebrate cats in the course of artificial supercooling. At a body temperature of 25° single stimuli evoked repeated discharges of motor neurons; at still lower temperatures, there was a spontaneous tetanic discharge of impulses both in the anterior and posterior roots. Hyperactivity at a low temperature is not associated with an increase in the excitability of the brain elements, inasmuch as the thresholds of their direct stimulation not only failed to decrease but even increased. The rate of transmission along the intracerebral pathways slowed down as did the development of stimulatory processes in the region of the synaptic connections. With cooling below 20° depression and total blockage of reflex activity occurred.

Hypothermia caused by physical cooling as well as its combination with neuroplegic preparations is accompanied not only by functional disturbances involving nervous activity but also pronounced morphological changes in various nerve structures. The changes in the gangliar cells of the brain took the form of tigrolysis or a coarsening of the tigroid substance. In addition to these mild and reversible changes, there was total dissolution of the tigroid with vacuolization and liquefaction of the gangliar cells (Meuller, 1954).

T. G. Zherebchenko (1953), together with I. A. Peymer, in experiments involving electroencephalograph (EEG) recordings found that during hypothermia there is quite a rapid disappearance of the rhythm with a frequency of 6-9 oscillations per second and development of slow waves with a frequency of 1-3 oscillations per second, i.e., a delta rhythm which indicates excessive inhibition in the cortex.

According to the data of Cazzullo, Quareschi, and Vitale (1954), the EEG rhythms during cooling slowed down, the waves grew less pronounced, and there was sometimes unclear and irregular. The study of G. Sh. Vasadze and Ts. Sh. Dzhanelidze (1969) confirmed that as hypothermia develops, with a decrease in the level of evoked responses in the cortex, there is an increase in the latter in the subcortical specific nuclei, extending as far as prevalence over cortical nuclei. On the basis of this observation it was assumed that there is a liberation of the nuclei of the visual tuber due to the decrease in the inhibiting influence of the cortex. Inhibition of the spontaneous and evoked activity of the reticular formation of the midbrain which occurs comparatively early, as does the loss of the negative component from the primary response, indicated to the authors that there was a blockage in stimulus transmission during supercooling, particularly in the nonspecific pathways. With low degrees of cooling (35-33°) the background rhythm accelerates and decreases its amplitude in the cortex and nuclei of the hypothalamus, reactions to individual stimuli undergo virtually no change, and the type of evocation of the rhythm of light flashes toward less pronounced liberation of relatively /24
high frequency changes, which can be evaluated as an increase in the general excitable process with insignificant decrease in the reactivity of the brain (S. N. Petrenko, 1969).

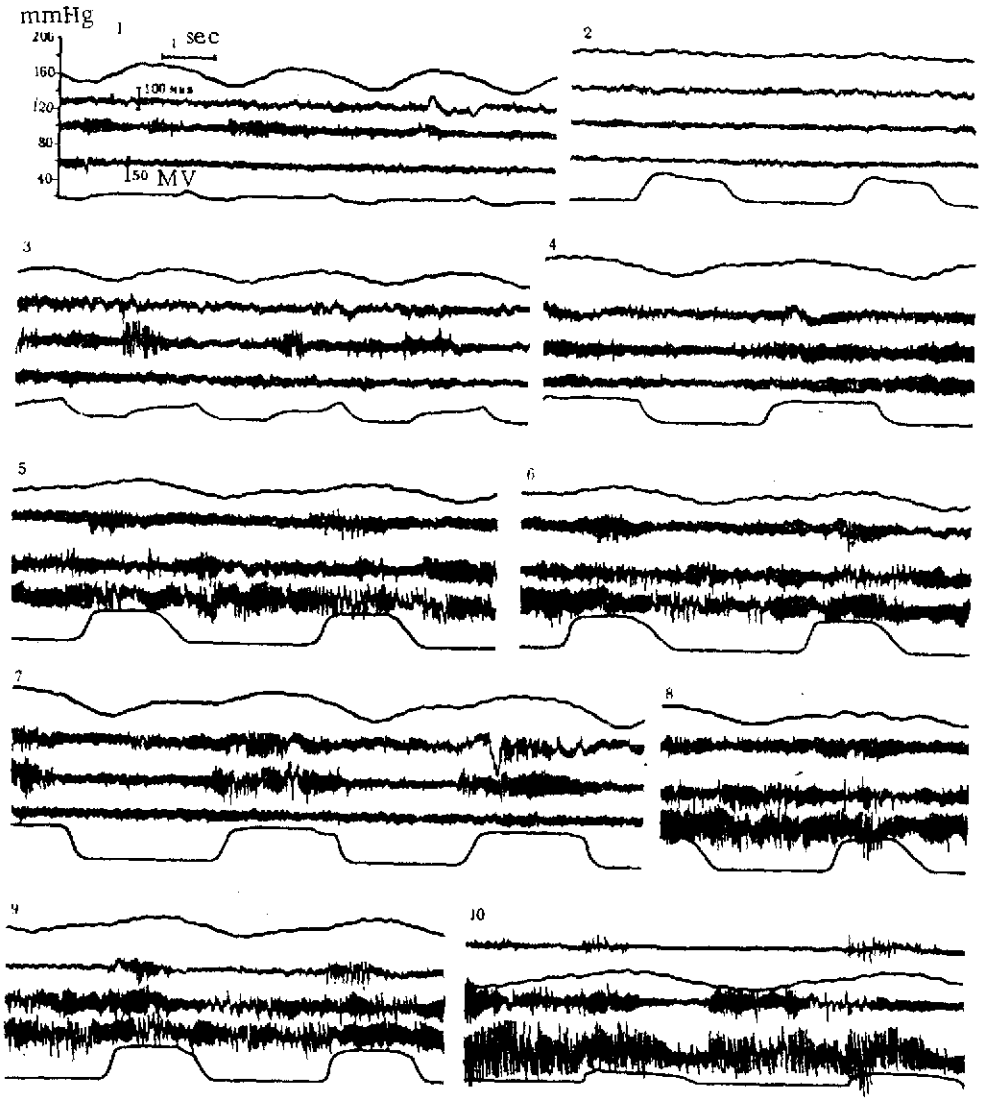

Figure 52. Changes in the Bioelectrical Activity of the Cerebral Cortex, Neurograms of the Vagus and Sinus Nerves in the Dynamics of Hypothermia

(See key to Figure 52 on next page.)

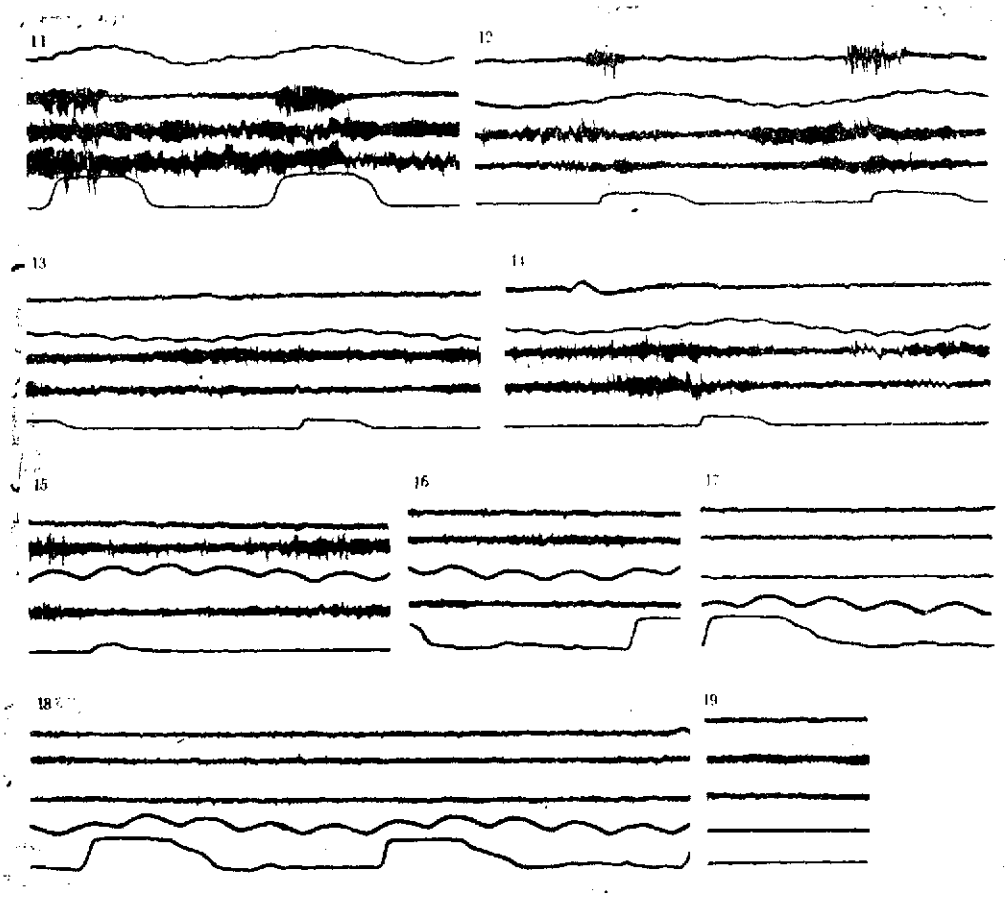

Figure 52 Key.

1, Initial background (at a body temperature of 36.8°); 1-19, Various periods following packing in ice; 2, After 3 minutes; 3, After 20 minutes (34°); 4, After 40 minutes (32.6°); 5, After 1 hour and 25 minutes (30.4°); 6, After 1 hour 40 minutes (29.7°); 7, After 2 hours (28.4°); 8, After 2 hours 30 minutes (27.2°); 9, After 2 hours 45 minutes (26.6°); 10, After 3 hours 20 minutes (25.6°); 11, After 3 hours 40 minutes (25°); 12, After 4 hours (24.3°); 13, After 4 hours 15 minutes (24.0°); 14, After 4 hours 25 minutes (23.6°); 15, After 4 hours 30 minutes (23.2°); 16, After 4 hours 40 minutes (23°); 17, After 4 hours 45 minutes (22.7°); 18, After 4 hours 48 minutes (22°); 19, After 4 hours 49 minutes (22°). From bottom to top: Blood pressure; Electroencephalogram (temporal region; Electroneurogram (vagus nerve); Electroneurogram (sinus nerve); Respiration; Zero mark.

The results of simultaneously recording the bioelectrical activity of the sensory conductors and various branches of the cerebral cortex with parallel oscillographic recording of blood pressure and respiration by means of a six--channel recorder (Figure 52) enabled us to conclude that the electrophysiological changes initially arise in the sensory conductors of the skin, almost simultaneously in the cortex, and are then recorded as disturbances involving hemodynamics and respiration. The next branch is the stimulation of the numerous vascular receptors and particularly their accumulations in the form of special reflexogenic zones, so that later there are pronounced changes in the electroneurograms not only involving the volley oscillations, but also involving the intervolley bioelectrical activity. The results obtained a second time indicated that in addition to the changes in the configuration of the volley, which furnishes delicate characterization of the minor oscillations in blood pressure, signalization from the sinus and vagus nerves informs the centers regarding more pronounced changes in pressure, chemism and blood temperature at the periphery, changing to continuous impulsation. This /245
probably takes place as a result of the more pronounced stimulation of the receptors which generate high-frequency impulses (Figure 53).

Hence, the initial changes involving the bioelectric activity of the cerebral cortex depend upon pronounced and continuous impulsation from the exteroreceptors, which are in contact primarily with a cold stimulus. The stimulation which occurs in the higher center sections of the central nervous system leads to changes involving the hemodynamics, respiration, and other functions of the organism. Subsequently, impulsation from the angioreceptors and the receptors of the internal organs constitutes a second powerful stimulus to the functional changes in the intact organism. The Interoreceptors are stimulated as a result not only of temperature but also of biochemical, physical chemical and other changes. To summarize these electrophysiological data, we can state that if the organism reacts to the general effect of cold by reflex methods and the changes observed during the initial stages express the inclusion of latent and compensatory accommodations, the stage of deep hypothermia involves disruption of the neuro-reflex regulation which can be considered the principal cause of development of the complex set of symptoms observed in the lethal period of hypothermia. The onset of hypothermia is accompanied by initial dyssynchronization and an increase in the total bioelectrical activity. A further drop in temperature is characterized by a decrease in electrophysiological excitability, for example in response to a sound stimulus with a 2-3° drop in body temperature. Particular attention /246
should be paid to the part of the EEG recording respiratory rhythm, where total areactivity of the cortex occurs even before the respiratory rhythm appears in the EEG. As the general cooling becomes more intensive, the respiratory rhythm is replaced by depression of the biopotentials. In the sublethal and particularly the lethal periods of hypothermia, the EEG flattens out altogether, failing to react either to sound or light.

An analysis of the "reactivity curves" has shown that during the initial decrease in body temperature there is an increase in excitability and an increase in the intensity of the reactions of the critical elements in response to stimulation of the auditory analyzer by a sound of increasing intensity (Figure 54, a, b). The type of curve frequently assumed an excitatory

character. When the body temperature fell by 3-5° the reaction to the sound stimulus was absent (Figure 54, c, d). According to the data of M. B. Shtark, the desynchronized electrical activity is least resistant to a decrease in intracerebral temperature. Consequently, the activity of the brain, particularly its enzyme systems, is limited to a rather narrow temperature range (not below 27°).

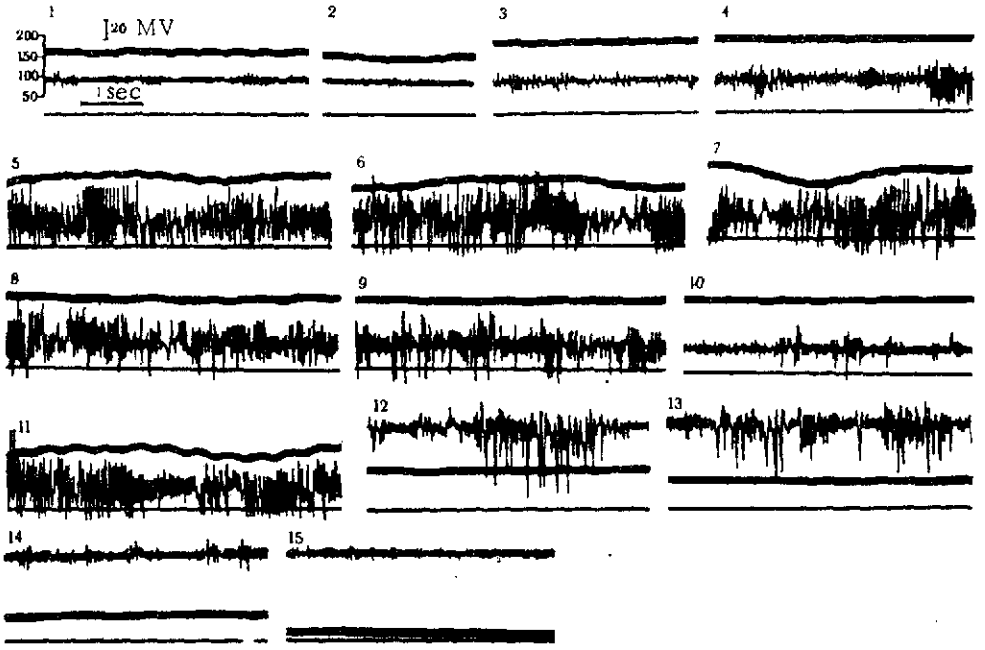

Figure 53. Electroneurogram of the Sinus Nerve During the Dynamics of Hypothermia
1, Initial background; 2-15, At various periods following application of ice; 2, After 2 minutes; 3, After 5 minutes; 4, After 10 minutes; 5, After 20 minutes; 6, After 30 minutes; 7, After 40 minutes; 8, After 1 hour; 9, After 1 hour 20 minutes; 10, After 1 hour 30 minutes; 11, After 1 hour 40 minutes; 12, After 1 hour 50 minutes; 13, After 2 hours; 14, After 2 hours 15 minutes; 15, After 2 hours 17 minutes. Top to bottom: blood pressure of the electroneurogram; Zero mark.

These dynamics, in conjunction with basic physiological processes in the central nervous system, are reflected in the changes in the bromine level as found in the arterial blood and the venous sinus of the brain. The initial insignificant cooling is accompanied as a rule by a decrease (and in more profound hypothermia with body temperatures of 25°, 23° and 22°, by a sharp increase) in the bromine content (Table 17).

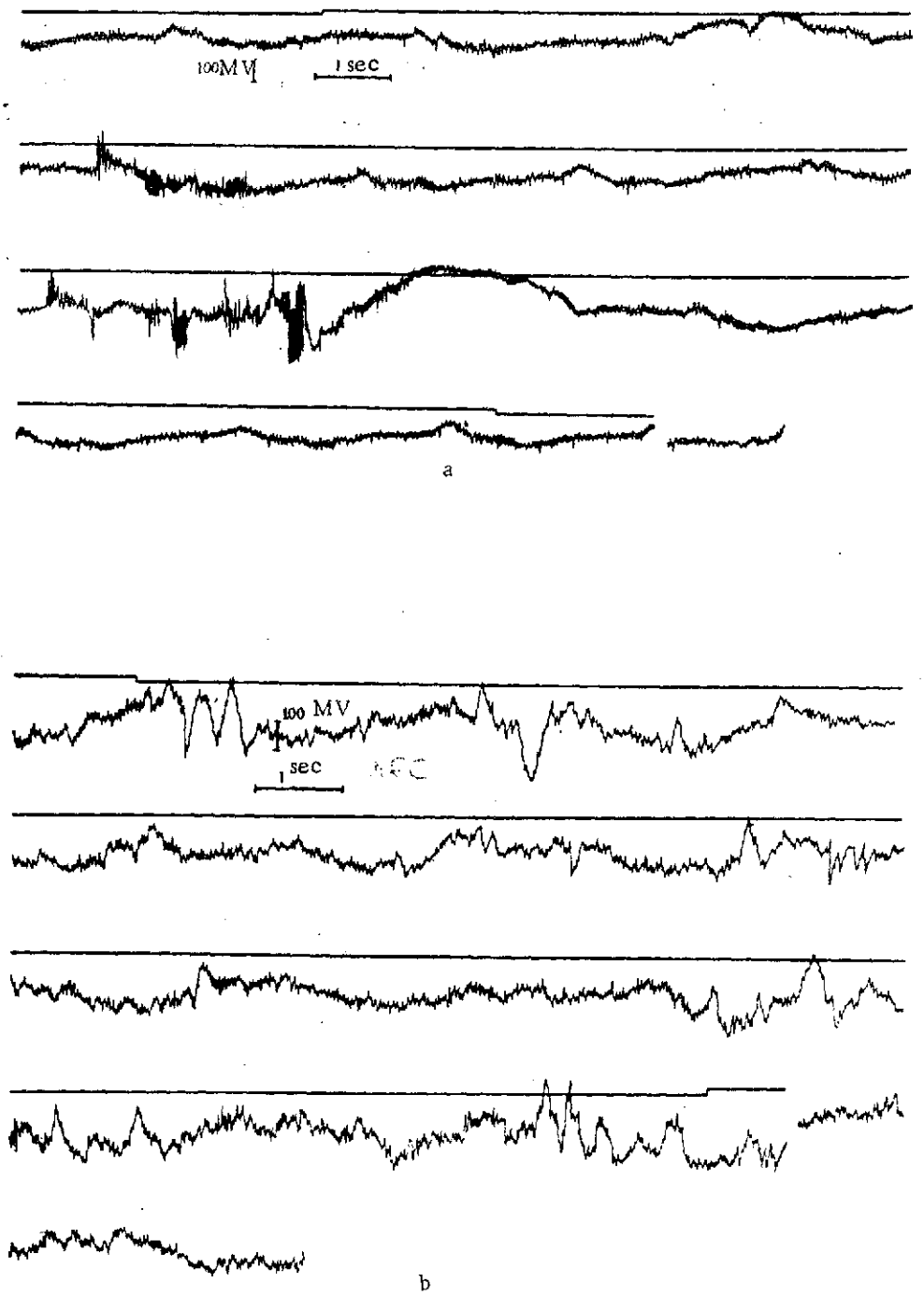

Figure 54. Electrophysiological Curves of Reactivity According to M. N. Livanov (in Response to a Sound Stimulus)

(See key to Figure 54 on the next page)

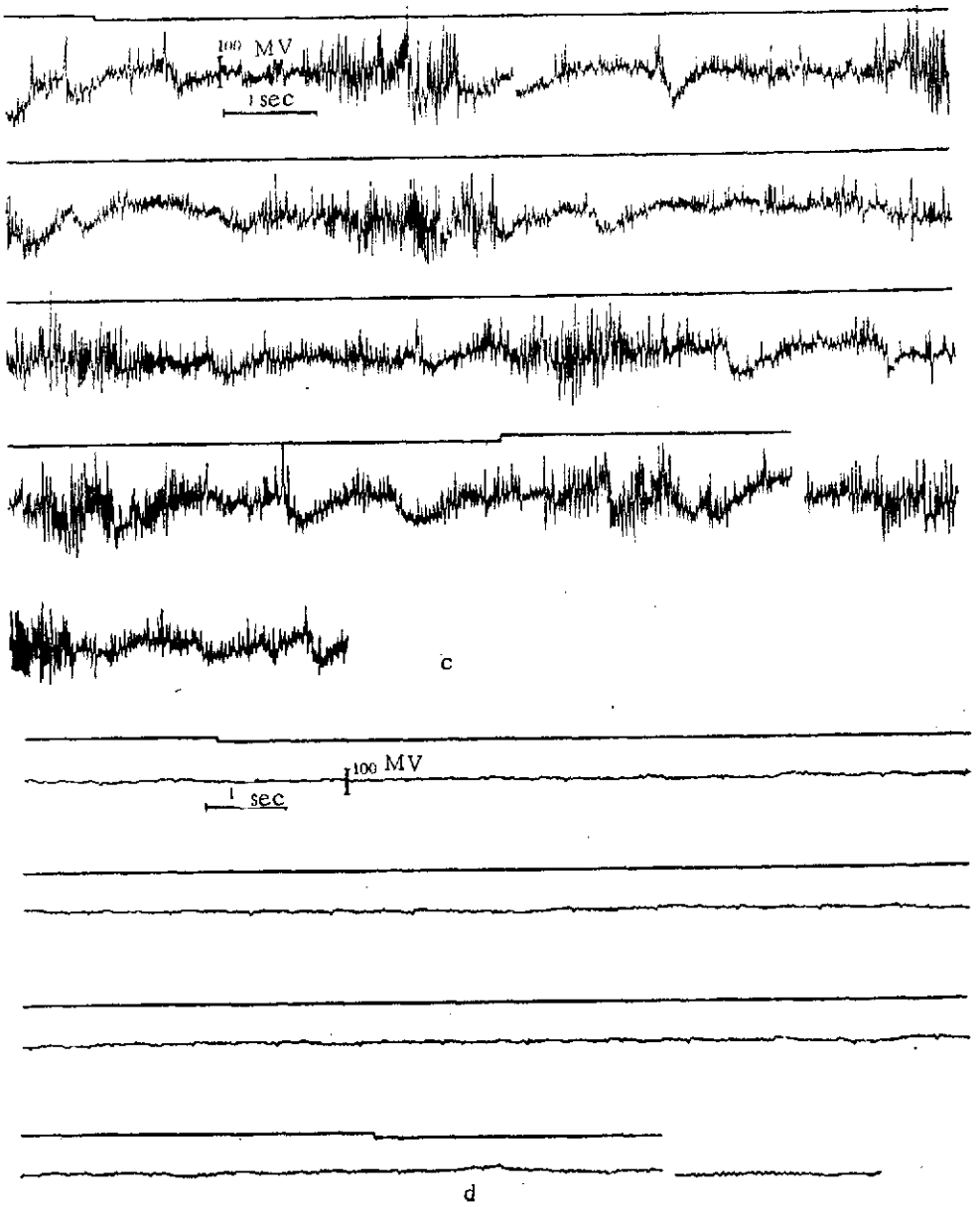

Figure 54 Key

a, Before Cooling; b, Following insignificant general cooling; c, Ataabbody temperature of 31.6°; 2, At a body temperature of 23°.

Disruption of the activity of the central nervous system during hypothermia is linked to a gradual development in various parts of it of an inhibition process. In the opinion of I. R. Petrov and Ye. V. Gubler (1961),

protective inhibition in the nervous system increases the resistance of animals to cerebral anemia and other forms of oxygen insufficiency. At more profound stages of hypothermia, it changes to the trans-threshold variety. The majority of authors feel that the inhibition that occurs during hypothermia is caused by specific direct effects of low temperature upon the nerve centers.

TABLE 17. BROMINE CONTENT IN THE BLOOD FLOWING TO AND FROM THE BRAIN IN VARIOUS PHASES OF HYPOTHERMIA (IN mg %)

Experimental Conditions	Parameters of Statistical Analysis	In The Arterial Blood	In The Venous Blood	Arteriovenous Differential
Initial temperature	M ± m	0.89 ± 0.15	0.85 ± 0.16	0.24 ± 0.08
With a decrease of 1-2°	M ± m	0.45 ± 0.17	0.62 ± 0.17	0.3 ± 0.06
	P	< 0.001	< 0.001	< 0.001
At a temperature of 32-30°	M ± m	1.17 ± 0.42	0.92 ± 0.24	0.47 ± 0.38
	P	< 0.001	< 0.008	< 0.001
At a temperature of 25-20°	M ± m	1.68 ± 0.15	1.21 ± 0.16	0.53 ± 0.24
	P	< 0.001	< 0.001	< 0.001

Considerable theoretical and practical interest surrounds the problem of hypothalamic (nerve-conductor and, particularly, neuro-humoral) links and the integration of vegetative functions during hypothermia. In recent years, /24
Ye. V. Maystrakh (1969) et al. (V. A. Karlov and P. P. Semenov, 1966; V. D. Zharskaya and Ye. Ye. Oksova, 1967; S. N. Petrenko, 1969) have obtained data indicating that the nuclei of the anterior hypothalamus are functionally and morphologically involved in the process of general cooling of unanesthetized animals. There are some papers by Italian authors who studied the histo-functional characteristics of the hypothalamic-hypophyseal system in experimental hypothermia. In the work of Monaci and Nocentini (1954) hypothermia in rabbits was accompanied by varying degrees of functional activity of neurons of /24
the anterior hypothalamus with a significant degeneration of the latter, and dilation of the lumina of the vessels. Azzali (1954), after producing hypothermia in dogs, failed to observe any changes in neurosecretion and its distribution by means of histological examinations, and on this basis he concluded that no serious role was played by the diencephalo-hypophyseal system in the pathogenesis of hypothermia. On the other hand, A. N. Buldakova (1967), keeping rats under conditions of a low ambient temperature (from -7 to -9°) noticed a predominance of excretion processes of neurosecretory granules over their synthesis, which in the final analysis led to functional exhaustion of the neurons. We have shown that 5-10 minutes following immersion in ice there is significant stimulation of the hypothalamic neurosecretion processes in the supraoptical and paraventricular nuclei of the anterior hypothalamus with an increased blood flow along the axons and accumulation in the neurohypophysis. There is alo a significant increase in the size of the secreting surfaces of the cell bodies and diameters of the nuclei in comparison with those of intact animals (Table 18).

TABLE 18. DIAMETERS OF THE NEURONS AND THEIR NUCLEI (IN MICRONS) IN THE SUPRAOPTICAL AND PARAVENTRICULAR NUCLEI OF THE ANTERIOR HYPOTHALAMUS IN HYPOTHERMIA (AVERAGE DATA FOR 20 CELLS)[1]

Effect	Supraoptical Nuceleus		Paraventricular Nucleus	
	Neuron	Nucleus	Neuron	Nucleus
Intact animals	25.3 ± 1.4	12.8 ± 0.4	22.7 ± 1.0	12.5 ± 0.8
5-10 minutes following immersion in ice	55.6 ± 0.7	20.9 ± 0.8	46.3 ± 0.7	20.4 ± 0.7
2° drop in body temperature	58.8 ± 1.4	21.7 ± 0.7	52.1 ± 1.7	22.1 ± 0.9
Drop in body temperature to 25°	61.8 ± 0.9	23.7 ± 0.7	48.9 ± 1.1	20.3 ± 0.6
Death of animal due to hypothermia	44.7 ± 0.3	36.6 ± 0.3	39.7 ± 0.7	32.2 ± 0.8

[1]The results of micrometry of the neurons in all groups of the experiments indicate a statistically reliable variation in size ($P < 0.001$).

These changes were less demonstrative in the neurons of the paraventricular nuclei. They were in a state of different functional activity with symptoms of increased and slightly pronounced neurocrinia while the neurons of the supraoptical nucleus were characterized by concomitant hypersecretion (Figure 55). The adenohypophysis showed symptoms of moderate hyperplasia of the basophilic cells, which exhibited intensive aldehyde-fuchsinophilic granularity. When the body temperature fell by 2-3° these secretory changes became progressive.

With a further drop in body temperature to 25-26°, together with an increase in the intensity of excitosecretory processes, there were still more severe dystrophic changes in the neurons. The tigroid almost completely disappears from the cytoplasm or becomes spotted with a considerable accumulation of neurosecretion (Figure 56). The sharply dilated axons and dendrites contact one another, with bodies of neurons and numerous dilated capillaries in the territory of the nuclei. Along the axons, in the paraventriculo-supraoptical tract numerous distentions and calluses of secretory material develop. In the hypophyseal stem and the neurohypophysis, large amounts of Gerring bodies appear and there is a pattern of "hypophyseal tomenta" which forms in the distal segment of the principal posterior portion of the boundary with the intermediate lobe. /250

In the terminal stage of hypothermia, with spontaneous onset of a terminal stage, the dystrophic changes in the neurons predominate. Mass corrugation of cells and pyknosis of the nuclei leads to a significant decrease in size of cell bodies and inhibition of their functional capacities. It is characteristic that the reaction involving the beta-basophilic cells of the adenohypophysis is retained intact. The secretion content in the neurohypophysis, i.e., in the region of deposition, is also quite high.

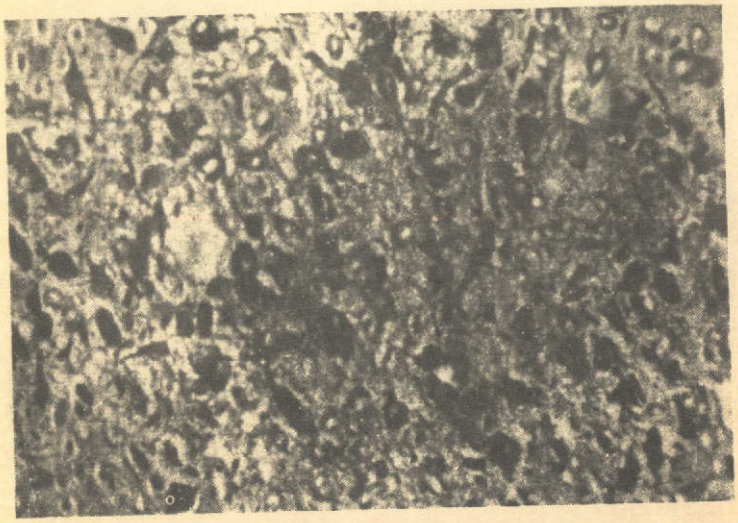

Figure 55. Supraoptical Nucleus. General Appearance of Sharply Increased Neurons, Overfilled with Neurosecretion. Stained according to Homori in the modification of V. F. Mayorova. Eyepiece 10, Objective 10 X.

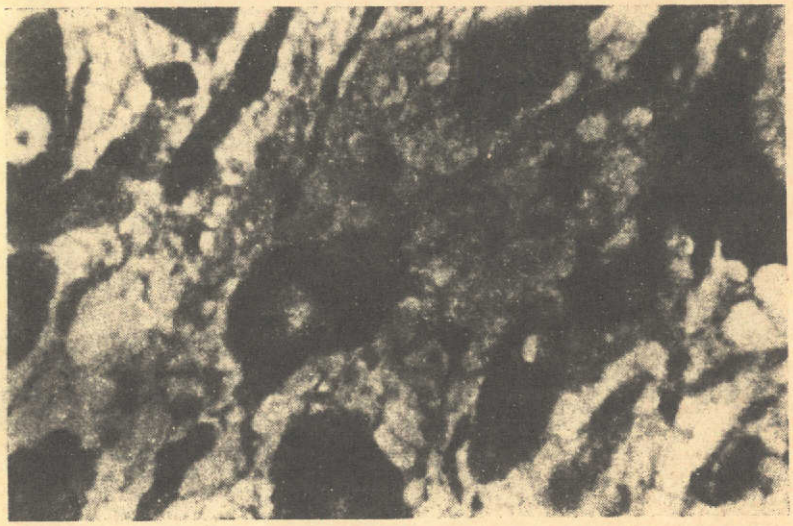

Figure 56. Supraoptical Nucleus. Increase in Functional Activity of Neurons With Increased Production and Efflux of Neurosecretion. Stained according to Homori in the modification of V. F. Mayorova. Eyepiece 10, Objective 40.

In the cortical substance of the adrenals, at all stages of hypothermia, one can see symptoms characteristic of the development of the stress syndrome (E. S. Yusfina, 1963; P. F. Zdrodovskiy, 1961 et al.). The most reliable symptom is an impoverishment of ascorbic acid in the fascicular zone, its progressive delipoidosis, thinning of the cortex with restructuring of the glandular elements of the fascicular zone in the bright-cell type. In the cortical substance, the chromophilic elements are impregnated in significant numbers and with a considerable degree of intensity even with cooling to 25-26° (E. S. Gul'yants, 1966-1969).

An increase in the content of cortical hormones of the adrenals in the blood leaving the organ (N. A. Yudayev et al., 1957) and their metabolites in the peripheral blood (Boulouard, 1959) and urine (Schapiro et al., 1958) indicate that cooling is accompanied by an increase in the production and excretion of corticosteroids. Swan et al. (1957), studying the content of corticosteroids in the blood and urine of patients who had been operated upon under hypothermia, observed an increase in the level of 17-hydroxycorticosteroids during cooling. N. A. Yudayev, Yu. A. Pankov and N. P. Surikova (1957), showed in experiments on rabbits that when

cooling takes place there is an increase in the content of corticosteroids in the blood of the adrenal vein due to the 17-hydroxycorticosterone, which indicates not only a stress effect of cold but also the possibility of a change in the type of steroidogenesis during hypothermia. In the opinion of the authors, hypothermia in all probability causes changes in the organism leading to increased consumption of this hormone. This assumption seems all the more likely since 17-hydroxycorticosterone increases the resistance of the organism to low temperatures. /251

In contrast to this, it is necessary to dwell on the studies of a number of authors who observed a decrease in the secretion of corticosteroids under the conditions existing during hypothermia. Egdahl et al. (1955) observed a decrease in the concentration of 17-oxycorticosteroids in the blood of the adrenal vein from 18 to 2 micrograms % with a drop in body temperature to 25-28°. During subsequent heating, the level of the corticosteroids returned to 22 micrograms %. Local cooling of the adrenals with general normothermia also caused a significant drop in corticosteroid secretion, which demonstrates the dependence of synthesis and secretion of hormones upon the level of metabolic processes in the gland. Gannong et al. (1955) feel that the corticosteroid balance in the organism is largely a reflection of the decrease in circulation of the blood through the adrenals observed by these authors. In this connection, however, it should be pointed out that the level of secretion of the hormones from the adrenal cortex is not directly related to the volume velocity of blood flow through the gland (Hayes, 1954; Frank et al., 1955). Some authors mention the decrease in total exchange of circulating blood during hypothermia as a possible cause of the changes in the concentration of the corticoids in the plasma (Barlow et al., 1959; Bigelow et al., 1961).

When we compare the experimental data observed by various authors in studying the function of the adrenal hypophesis and cortex under conditions of hypothermia, we have to take into account the fact that the reaction of these glands to the harmful effects of low temperature is largely governed by the period of observation, the presence or absence of medications, the degree of hypothermia, and so forth. Thus, A. I. Yakovleva (1964), observing the action of cold against a background of a preliminary administration of aminazine, found a more pronounced drop in the adrenal cortex ascorbic acid content than in animals who were subjected only to cooling, although the body temperature in the case where aminazine was used was much lower. N. A. Khaug and Kh. K. Turu (1965), studying the morphological changes in the adrenal cortex, concluded that the stressor effect of general cooling of the organism under conditions of a potentiating anesthetic are manifested only weakly. /252

Laborit and Huguenard (1954), in summarizing their own data plus data in the literature, pointed out that following "neuroblockade", cooling fails to evoke a reaction involving the hypophysis and the adrenals, and consequently hypothermia is not a stimulus.

The data from the literature relative to the status of the cortical layer of the adrenals and the sympathetic nervous system during hypothermia are also somewhat contradictory. Histochemical methods failed to reveal any significant changes in the medullar zone of the adrenals with regard to the content of

chromassinic substance when rats are cooled to 18-23° (Fischer et al., 1955). Tigyi, Puppi, and Lissak (1959) observed a significant drop in the adrenaline and noradrenaline content in the adrenals of rats subjected to cooling. Hume and Egdahl (1959), when they reduced the body temperature of dogs to 20-28°, observed a progressive decrease in the blood adrenaline and noradrenaline content. In addition, Mitsumi (1960) points out that hypothermia considerably reduces only the adrenaline level and has almost no effect on the noradrenaline content. Moreover, Brown and Cotten (1956) working with deep hypothermia in dogs, found an increase in the concentration of adrenaline and noradrenaline in their blood. Data obtained by G. M. Solov'yev et al. (1964) with hypothermal perfusion with a barbiturate anesthetic, concluded that during the period of cooling there is a blockage of the adrenoreactive systems. N. V. Korostovtseva (1959) found that in deep anesthetic inhibition of the central nervous system, hypothermia in dogs and rats is not accompanied by increased secretion of adrenaline and noradrenaline. Deeper hypothermia (26-27° in dogs and 8-9° in rats) causes the cortical substance of the adrenals to weaken.

G. M. Darbinyan, Ye. P. Stepanyan and G. O. Andzhelov (1965), studying patients who had undergone surgery with an injected anesthetic, curarization and hypothermia, found that the blood adrenaline concentration decreased while the noradrenaline concentration increased 3-5 minutes after the beginning of cooling. With maximum cooling (23-28°) there was a drop in the total catecholamine content, mainly due to the further drop in the adrenaline content. In the absence of adequate relaxation, the same authors found sharp activation of the sympathetic-adrenal system in response to cooling. While the effect of the relaxant during the cooling process weakened previous attainment of moderate hypothermia, the recovery of the patient from relaxation was characterized by significant increases in the catecholamine level.

The studies performed by S. A. Yeremina (1967) showed that the development of hypothermia is accompanied by changes in the functional state of the hypothalamic-hypophyseal-adrenal and sympathetic-adrenal systems. These /253
experiments were performed on male dogs. Hypothermia was produced by submerging the unanesthetized animals in an ice bath. Fractional determination of the protein-bound and free forms of 11-HCS was carried out, measurement of the content of 11-HCS in the tissues, the content of catecholamines and serotonin in the blood and tissues.

Submersion of the animal in the ice bath causes the level of corticosteroids to rise although the body temperature has not yet changed (Table 19).

Subsequently, while the rectal temperature fell, the content of corticosteroids continued to rise. The degree of cooling and the severity of the cortical reaction of the adrenals are parallel until a body temperature of 25-26° is reached. More pronounced hypothermia causes a drop in the concentration of corticosteroids in the plasma.

The content of total 11-HCS theoretically coincided with the concentration of 17-HCS during the development of hypothermia. A significant increase in the level of free 11-HCS with insignificant changes in the contents of protein-bound corticosteroids was only observed with moderate hypothermia. With a

decrease in body temperature to 25-26° or less, there was a sharp increase in the percentile and absolute content of protein-bound 11-HCS with a simultaneous decrease in the concentration of free corticosteroids. Hence, the state of deep hypothermia, especially its terminal phase, is characterized by a significant increase in the binding of circulating corticosteroids with protein. The author considers the most probable cause of this phenomenon to be the disruption of protein metabolism and physical-chemical state of protein during cooling. The biological significance of the increase in the protein binding of corticoids in the state of deep hypothermia, in which the energy expenditure of the cells decreases, is viewed in a distinctive "reservation" of hormones, protecting them against inactivation in the liver. The content of corticosteroids in the tissues of the central nervous system (the region of the hypothalamus and the frontal lobe) and the myocardium in the initial phase of hypothermia increases moderately, while in the case of significant cooling they drop to subnormal levels. The quantity of corticosteroids in the cortical substance of the adrenals decreases progressively with an increase in the degree of hypothermia, suggesting inhibition of steroid hormone synthesis under the influence of cold.

TABLE 19. CONTENT OF CORTICOSTEROIDS IN BLOOD PLASMA (IN MICROGRAMS %) IN THE DYNAMICS OF HYPOTHERMIA

Parameters	Original Background	Following Submersion in ice	With Drop of Temperature by 1-2°	30-32°	25-26°	Thermal Period
17-HCS	12.3±1.1	22.0±2.6	22.7±3.7	24.6±2.3	32.3±4.1	14.6±2.9
Total 11-HCS	21.1±1.8	28.4±2.0	31.4±2.3	36.3±2.4	36.7±2.7	31.9±3.4
Free 11-HCS	5.7±1.4	12.5±1.4	14.0±1.2	20.3±2.1	5.2±1.3	3.7±1.2
Protein-bound 11-HCS	15.4±0.7	15.9±0.7	16.1±1.0	15.7±0.8	31.6±2.0	28.3±2.8
Percentage of bound corticosteroids	75.6±4.8	57.0±2.3	51.9±2.3	44.3±2.9	87.1±3.0	89.8±2.9

Preliminary administration of aminazine (2.5-3 microns/kg intramuscularly 30-40 minutes prior to submersion of the animal in ice) significantly altered the reaction of the adrenal cortex to the influence of cold (Table 20).

TABLE 20. 17-HCS CONTENT IN BLOOD PLASMA (IN MICROGRAMS %) ACCOMPANIED BY THE DEVELOPMENT OF HYPOTHERMIA AGAINST THE BACKGROUND OF ACTION OF AMINAZINE

Initial Background	Following Administration of Aminazine	Following Submersion in ice	With a 2° Decrease in Temperature	30-32°	25-26°	Terminal Period
16.1 ± 2.0	19.6 ± 1.6	34.3 ± 2.2	19.6 ± 2.1	20.9 ± 1.6	19.9 ± 1.5	8.1 ± 0.9

The mechanism of the blocking effect of aminazine on the formation of the response reaction of the adrenal cortex has nothing to do with the direct action of the preparation on the gland, since the administration of exogenic ACTH against the background of aminazine action causes a significant increase in the 17-OCS content in the plasma (S. A. Yeremina, 1967). The fact that adrenaline has no activating effect on the hypothalamic-hypophyseal-adrenal system under the conditions of action of aminazine has enabled the author to conclude that the suppressant effect of aminazine is linked to the blocking effect of the preparation upon the adrenoreactive mechanisms of the reticular formation and the hypothalamus, exercising control over the adrenocorticotropic function of the hypophysis and glucocorticoid secretion in the adrenal cortex.

When the animal is submerged in ice against a background of constant body temperature, the level of noradrenaline in the blood rises and the adrenaline concentration falls (Table 21).

TABLE 21. CATECHOLAMINE CONTENT IN THE BLOOD (IN MICROGRAMS/LITER) IN THE DYNAMICS OF HYPOTHERMIA (M ± m)

Catecholamines	Initial Background	Following Submersion in ice	With decrease in temperature by 2°	30-32°	25-26°	Terminal Period
Adrenaline	1.54±0.22	0.51±0.10	3.01±0.41	3.59±0.36	1.08±0.25	22.70±7.27
Noradrenaline	3.92±0.25	11.40±1.70	3.02±0.61	2.49±0.67	7.30±1.22	1.65±0.87

With weak and moderate cooling (36-30°) the adrenaline content increases by a factor of 2 while the noradrenaline content drops to subnormal levels. Cooling to 25-26° is accompanied by a secondary elevation of the concentration of noradrenaline with parallel decrease in the adrenaline content. In the terminal phase of hypothermia there is a significant drop in the noradrenaline level, which in some experiments is even absent in the blood. At the same time, there is an influx of massive amounts of adrenaline into the blood whose concentration increases by nearly 15 times on the average. This phenomenon is not specific to this phase of hypothermia, inasmuch as the terminal period of shock, with different etiology, is also characterized by a significant accumulation of adrenaline in the blood with a parallel drop in the noradrenaline level (S. A. Yeremina et al., 1967). Data on the distribution of catecholamines in the tissues of the central nervous system, the cortical substance of the adrenals, and the myocardium are of interest in the dynamics of hypothermia (Table 22).

Following submersion in an ice bath of 5-7 minutes, the anterior and posterior lobes of the hypothalamus show a marked decrease in noradrenaline content with a simultaneous increase in the quantity of adrenaline. In the initial phase of cooling (with a 2° drop in body temperature) the level of the

/25

noradrenaline in the hypothalamus returns nearly to the original values, and the adrenaline concentration at the same point in time decreases in the tissues of the anterior and particularly the posterior hypothalamus. In deep hypothermia (25-26°) there was a secondary increase in the adrenaline content and a drop in the noradrenaline content in the tissues of the hypothalamus. In the terminal period the catecholamine concentration in the tissues of the hypothalamus is lower than background values.

The cerebral cortex has been found to show a significant increase in the catecholamine content, particularly the adrenaline, at all stages of cooling, including the terminal period.

The cortical substance of the adrenals, in the case of mild cooling, shows a slight increase in the quantity of adrenaline, while the amount of this substance drops sharply with deep hypothermia. A significant increase in the noradrenaline content in the medullary zone of the adrenals is characteristic of all stages of cooling, indicating a certain degree of "stress" of the adrenaline synthesizing process.

During the development of hypothermia, the cardiac muscle has a progressively increasing adrenaline level with a simultaneous decrease in the amount of noradrenaline. The latter suggests a disruption of catecholamine metabolism in the myocardium during cooling. /25

These data indicate that the primary reaction to the cooling process is characterized by mobilization of noradrenaline by the hypothalamus and accumulation of adrenaline in the tissues of the central nervous system. In deep hypothermia, adrenaline synthesis in the cortical substance of the adrenals is disrupted.

In analyzing the factual material obtained, it is necessary to remember that the heat regulation reactions of the hypothalamic centers are accomplished by a change in equilibrium between the catecholamine concentrations in the diencephalic region (Feldberg, Myers, 1963). It is felt that the biogenic amines are specific regulators of chemical thermogenesis. The high degree of significance of catecholamines and serotonin in hypothermia pathogenesis is indicated by the fact that there is a reduction of thermostability in dogs treated with reserpine, which exhausts the tissue deposits of monoamines (S. A. Yeremina, Ye. P. Mezhera, 1969). The data obtained in our laboratory (Table 23) also showed that the development of hypothermia is accomplished by a decrease in the serotonin level in the blood and phase changes in its content in the tissues.

Cardiovascular system and respiration. The first experimental data on the influence of cold upon the heart were presented by P. Zabolotskiy (1855) who found that as the body temperature falls the activity of the heart grows weaker. A similar conclusion was reached by A. P. Val'ter (1863), A. Khorvat (1870, 1872), and G. G. Skorichenko (1891). The most significant harmful effect of cold upon the heart was found when the body temperature fell to 32-30° (Giese, 1901). Later, Hoffman (1925) found that after breathing ceases, as a result of deep cooling, the heart continues to beat for a certain time. Stehelin (1927) felt that hypothermia merely causes "temporary paralysis of the heart".

TABLE 22. CATECHOLAMINE CONTENT IN THE TISSUES OF THE CENTRAL NERVOUS SYSTEM, MYOCARDIUM (IN MICROGRAMS/G OF FRESH TISSUE) AND CORTICAL SUBSTANCE OF THE ADRENALS (IN MG/G OF FRESH TISSUE) IN THE DYNAMICS OF HYPOTHERMIA

Tissue	Catecholamines	Intact Animals	5-7 Minutes Following Submersion in ice	With a Temperature decrease of 2°	At a temperature of 25-26°	In the Terminal Period
Cortex of frontal lobes	Adrenaline	0.037 ± 0.005	0.410 ± 0.098	0.287 ± 0.031	0.164 ± 0.024	0.091 ± 0.027
	Noradrenaline	0.24 ± 0.03	0.30 ± 0.05	0.53 ± 0.08	0.33 ± 0.07	0.42 ± 0.07
Anterior hypothalamus	Adrenaline	0.21 ± 0.02	0.55 ± 0.06	0.19 ± 0.02	0.38 ± 0.08	0.18 ± 0.03
	Noradrenaline	0.79 ± 0.09	0.16 ± 0.03	0.67 ± 0.14	0.41 ± 0.10	0.36 ± 0.08
Posterior hypothalamus	Adrenaline	0.22 ± 0.02	0.45 ± 0.10	0.10 ± 0.01	0.25 ± 0.06	0.18 ± 0.02
	Noradrenaline	0.81 ± 0.08	0.26 ± 0.04	0.70 ± 0.09	0.39 ± 0.11	0.39 ± 0.09
Cortical substance of adrenals	Adrenaline	2.462 ± 0.197	3.144 ± 0.253	3.341 ± 0.340	1.770 ± 0.250	1.243 ± 0.161
	Noradrenaline	0.101 ± 0.044	1.200 ± 0.384	0.925 ± 0.116	1.080 ± 0.400	1.295 ± 0.526
Myocardium	Adrenaline	0.10 ± 0.02	0.09 ± 0.02	0.20 ± 0.05	0.16 ± 0.03	0.16 ± 0.05
	Noradrenaline	0.56 ± 0.10	0.30 ± 0.05	0.28 ± 0.04	0.29 ± 0.05	0.14 ± 0.03

TABLE 23. BLOOD SEROTONIN LEVEL (IN MICROGRAMS/ML) AND TISSUE LEVEL (IN MICROGRAMS/G OF FRESH TISSUE) IN DOGS UNDER THE DYNAMIC CONDITIONS OF ARTIFICIAL HYPOTHERMIA

Tissue	In Intact Animals	Following Submersion in Ice			
		With a decrease in temperature by 1-2°	30°	25°	Terminal Period
Blood	0.37 ± 0.05	0.37 ± 0.07	0.31 ± 0.07	0.23 ± 0.04	0.16 ± 0.03
Hypothalamus	0.84 ± 0.11	1.07 ± 0.06	0.98 ± 0.06	0.90 ± 0.04	0.78 ± 0.18
Cortex of frontal lobes of the brain	0.39 ± 0.08	0.33 ± 0.06	0.25 ± 0.02	0.61 ± 0.06	0.39 ± 0.08
Myocardium	0.36 ± 0.02	0.51 ± 0.07	0.31 ± 0.05	0.45 ± 0.07	0.22 ± 0.06
Liver	0.82 ± 0.06	0.78 ± 0.14	0.71 ± 0.07	0.90 ± 0.07	0.83 ± 0.09
Duodenum	4.17 ± 0.80	5.86 ± 0.73	3.60 ± 0.49	5.28 ± 0.74	4.76 ± 0.64

The data obtained by cooling human beings are of great value. D. P. Kosorotov (1911) found that cardiac activity at the beginning of cooling increases and gradually grows weaker only when the temperature rises. G. P. Shul'tsev (1945) and G. A. Orlov (1946) found pronounced bradycardia in persons /257 subjected to deep hypothermia. In the case of general cooling in man, the arterial pressure is characterized by low pulse pressure due to the drop in systolic pressure, while the diastole remains at a normal level.

Experimental studies performed on rabbits, cats and dogs (A. I. Yakobiy, 1864; A. A. Zubchenko, 1903; Giese, 1901) also indicated a progressive slowdown (parallel to the development of hypothermia) in the rhythm of cardiac activity. In addition, according to the data of Oppenheimer and McCravcy (1941), and V. I. Yegorov, Yu. N. Katmenskiy, and P. V. Ponomarev (1956), decreasing the body temperature to 32° or more caused a decrease in the minute and stroke volume. With still more pronounced hypothermia (up to 17°), the minute volume was 15% of the initial level (Hegnauer, D'Amato, Flynn, 1951). A. L. Izbinskiy (1949) found a drop in the minute volume of the heart to 66% of the background value when the temperature dropped to 15°. On the other hand, P. M. Starkov (1957), under the conditions of a heart-lung preparation, failed to observe any noticeable changes in the magnitude of the minute volume all the way down to a 25° decrease in body temperature.

According to the data from several authors, hypothermia is accompanied by a significant drop in the flow of blood to the heart (King, Bouhous, 1958).

As we know, the heart of a warm-blooded animal is capable of changing its activity as the body temperature drops, adopting a rhythm which corresponds to the rhythm of cold-blooded animals. This fact is of theoretical value in understanding complex processes that occur in vital systems during cooling

(L. I. Murskiy, 1958; V. A. Krasavin, 1961; Yu. A. Gogin, 1962, 1963; V. V. Suvorov, 1962; A. M. Malygin, 1963). An analysis of modern experimental and clinical data indicates that the normal reaction of the vessels of the internal organs to cold is a powerful spasm. The vessels at the surface of the body react to cold by a spasm followed by a reactive dilation.

In 1937, N. V. Puchkov found that an increase in arterial pressure, observed during initial cooling, is maintained after the adrenals are removed. On this basis, the author concluded that the increased blood pressure was caused by stimulation of the sympathetic nervous system. According to the observations of V. N. Sheynis (1941), arterial pressure begins to drop in rabbits only with extreme degrees of cooling. V. N. Chernigovskiy and N. N. Kurbatova found that a significant cutback (up to 50%) in blood flow takes place when the body temperature falls to +23°. Similar results were presented in the work of P. N. Veselkin (1943) and M. A. Shamshina (1943). The principal reason for the hemodynamic disturbances involved in cooling is the acute bradycardia causing the drop in the minute volume of blood circulation and, as the consequence of this, the drop in arterial pressure and circulation rate (M. A. Kondratovich, 1969). The hemodynamic disturbances also involve an increase in the total peripheral resistance to blood flow and inhibition of reflex regulation of the vascular tone.

Crisman (1944) isolated three phases in the changed blood circulation during hypothermia. He called the first phase "compensatory regulation of circulation"; here, spasms of the vessels are recorded, rhythm slows down, and the stroke volume of the heart increases. This phase was observed when the temperature of the body fell to 28°. During the second phase (body temperature 29-20°) there is a progressive drop in blood pressure and a slowdown of the pulse rate and minute volume. The third phase, referred to as the "regional asphyxiation", occurs in deep hypothermia (below 19°). In this /258
phase the heart stops, symptoms of asphyxia appear and respiration is impeded.

The dynamics of hypothermia can be seen to include distinctive and quite regular respiratory changes exhibiting periodicity which correlates with disturbances of cardiac activity. Respiration is initially rapid and deep, and then gradually slows down. P. M. Starkov (1947) found that, in the absolute majority of cases, adult dogs died much earlier than young animals, as a rule is due to primary cessation of respiration. T. Ya. Ar'yev (1943) and Ye. A. Zherbin (1950) observed that after breathing had stopped in supercooled animals the heart continued to beat in a very slow rhythm. The changes in the magnitude of pulmonary ventilation at the beginning of hypothermia were not regular, while in the case of deep supercooling (26-22°) the volume of inspired air decreased considerably in comparison with the initial values (Ye. V. Maystrakh, 1950).

There is considerable interest in the changes that occur involving venous pressure. It should be pointed out first of all that the change in venous pressure is one of the earliest and most sensitive indicators of an unfavorable course of hypothermia (P. A. Kupriyanov and B. S. Uvarov, 1956; N. I. Nikitina, 1956; A. L. Vilkovskiy et al., 1957; V. D. Malyshev, 1957). Submersion of unanesthetized animals into cold water causes a sharp increase in venous

pressure. Cooling them under deep anesthetic has no influence on the magnitude of the venous pressure, not even causing it to drop (Rosomoff, 1956). The instantaneous increase in venous pressure is a symptom of acute hypoxia of the myocardium or a reaction to cold with an insufficiently blocked nervous system (V. P. Ruban, 1956; L. I. Murskiy, 1958).

Metabolic processes. The literature contains a great many experimental data (P. M. Starkov et al.; Ye. V. Maystrakh, A. L. Izbinskiy et al.) and clinical observations (Ye. V. Gubler; Siemons, Bernemeier et al.) which indicate that there are significant disturbances in the metabolic process, especially oxygen consumption, during the development of hypothermia. From the results of these investigations, one can conclude that there is a direct relationship between the deep cooling process and the degree of decrease in the metabolic processes in the organism.

Still earlier efforts by Wetheim (1870), Pfluger (1876), Quinquand (1887) and Cassnier and Mayer (1935) showed that hypothermia involves a change in gaseous and energy exchange. According to the data of Dill and Forbes (1941), the initial stage of hypothermia in man is marked by an increase in the level of metabolic processes with a subsequent decrease in their intensity. Later these facts were confirmed repeatedly (Hutt, 1953; Osborn, 1953; Spurr, Hutt, and Horwath, 1954; Fleming, 1954; Hegnauer, and D'Amato, 1954; Cranston et al., 1954). A complex study of the metabolic state and of a number of other vegetative functions during hypothermia was carried out by P. M. Starkov and his colleagues who showed that the changes in the metabolic processes, particularly oxygen consumption, fall into phases. According to the results of A. L. Izbinskiy, the first phase of hypothermia is accompanied by a pronounced rise in oxygen consumption (150-180% of the original value). With a further decrease in temperature of the body from 33 to 29-27° (second phase), oxygen consumption exceeds the initial values by 2-3 times. When the temperature drops below 27°, the third phase of hypothermia develops, which is characterized by a decline in the metabolic processes. In the fourth phase (body temperature below 19°), the metabolic processes are sharply cut back. These characteristics of the change in intensity of metabolic processes are considered by A. L. Izbinskiy to be the result of a complex regulatory activity of the central nervous system. The nature of the change in the metabolic processes in the first three phases is a function not only of inhibition but of the development of an integrating function by the central nervous system. The decrease in the metabolic rate in animals, associated with actual inhibition of the central nervous system, takes place only in the fourth phase. /25

These facts are of theoretical significance in the light of the theories of V. N. Sheynis and many other researchers concerning the conversion of homothermal into poikilothermal animals at body temperatures of 26-28° or less. The experimental data of A. L. Izbinskiy leave no doubt as to the erroneousness of this assumption; he points out that when the body temperature drops to 20-19° the intensity of the metabolic processes is still governed to a large extent by the activity of the central regulatory apparatus.

The results of a study of the gas composition of the blood at various phases of hypothermia in white rats have shown a gradual increase in the

arterial and venous hypoxemia as the body temperature drops. Determination of the oxygen capacity and a study of the dissociation curves for oxyhemoglobin enabled A. L. Izbinskiy to assume that the affinity of hemoglobin for oxygen rose significantly as the hypothermia of the animals increased. A study of the arterio-venous differential with respect to oxygen (Rosomoff, 1956; Fairley, 1961) has hsown that it remains constant up to body temperatures of 25°. Consequently, a decrease in oxygen consumption by the brain takes place in parallel with a decrease in blood flow. However, the onset of acidosis symptoms in moderate hypothermia can be explained only by inadequate ventilation of the lungs (Terzioglu et al., 1959). Dropping the body temperature of homothermal animals causes a sharp decrease in oxygen and glucose consumption by the brain (Himwich et al., 1940; Field et al., 1944; Rosomoff, Holaday, 1954) and a lowered metabolism in the tissues of the brain. At the same time, the content of phosphorus compounds, glycogen, and lactic acid remained within the limits of the initial values (Newman, 1938; Fleming, 1954; Stefanovic, 1954; G. Ye. Vladimirov, 1957). Cooling anesthetized animals (using amytal-sodium and ether) causes a significant drop in the rate of replacement of all phosphorus compounds in the brain (G. Ye. Vladimirov, 1959). In the initial stages of cooling, there is a sharp drop in the amount of free glycogen, which is intensively involved in metabolic processes, while in the stage of "cold anesthesia" its content increases (N. G. Atabegova, L. I. Mishina, 1969). Under the conditions of deep hypothermia, ATP and CP* synthesis takes place quite intensively, showing good retention of the Pasteur effect (G. Ye. Vladimirov, 1967; O. N. Savchenko, 1958).

As the body temperature reverts to normal in animals after hypothermia, the rate of renovation of the phosphorus-containing compounds of the brain rapidly returns to normal. This indicates that artificial hypothermia is accompanied by inhibition and not damage to the enzyme and structural systems that participaye in phosphorus metabolism (G. Ye. Vlasimirov, 1959) and supports the ideas of A. L. Izbinskiy concerning the absence of any causal relationships between the death of highly-organized animals from supercooling and the exhaustion of the energy resources.

The detailed studies of N. G. Atabegova (1966, 1969) found differences in the reaction of macroergic phosphorus compounds of the brain on the effect of cold as a function of the type of nervous activity of the animals being cooled. In rats with predominance of the stimulatory process the initial breakdown of /260
these compounds is replaced by their accumulation in deep hypothermia. In rats with prevalence of the inhibitory process at all stages of hypothermia there is a gradual increase of labile phosphates in the brain. During the supercooling process, changes take place in the relationships between the macroergic phosphate systems in the brain; in particular, a great deal of unbalanced inorganic phosphorus is accumulated, and reesterification between CP and ATP takes place. The respiration of areas of the cerebral cortex gradually decreases.

At the beginning of cooling, oxidation and phosphorylization spread rapidly, while in the stage of "cold anesthesia" there is an increase in the intensity of the reactions involving oxidative phosphorylization. This is

*Translator's Note: CP = creatine phosphate.

accompanied by a transformation of certain types of mitochondria into others, the latter losing their ability to regulate the intensity of respiration.

At a body temperature of 37-31°, the oxidative processes in the liver and muscle tissues increase by a factor of 1.5-1.8, while at 31-27° they increase by a factor of 2-3; oxygen consumption by the brain tissue at this level of development of hypothermia does not change significantly (A. L. Izbinskiy, 1953). The respiratory coefficient approaches unity, indicating that predominant role is being played by carbohydrate metabolism (L. I. Murskiy, 1958). The mitochondria in the liver under these conditions show a tendency toward activation of respiratory and phosphorylizing ability (Ye. M. Khvatova, N. A. Shvets, G. S. Seroglazova, 1969). As the degree of hypothermia increases, the intensity of the oxidative processes sharply decreases, from which several authors conclude that it should be connected with the onset of "cold anesthesia" (Bigelow et al., 1950; Ye. V. Maystrakh, 1955). When the body temperature drops below 27°, the brain tissue begins to exhibit oxygen starvation (A. A. Kalikhman, 1953). The respiratory coefficient drops with increasing hypothermia to 0.62-0.47, indicating predominant metabolism of proteins and fats (Kh. A. Akhmetbekova, 1957; G. I. Burshteyn et al., 1958; L. I. Murskiy, 1958). Cooling to 20° or less causes a drop in gas exchange by a factor of 3.5 to 5 (Penrod, 1949; A. L. Izbinskiy, 1953; P. M. Starkov, 1955; Z. P. Kuznetsova, 1947); the brain tissue undergoes a considerable degree of oxygen debt (A. A. Kalikhman, 1953).

Blood system. Role of the harmful effect of cooled blood. Changes in the morphological composition of the blood during hypothermia are quite irregular, and the results obtained by various authors are partially contradictory (Friedlander, 1897; Reineboth, 1899; Kayser, 1913). N. V. Puchkov (1937) observed significant leukopenia during supercooling; this condition was particularly pronounced in rats and somewhat less in mice. The authors suggests that this kind of change occurs as the result of a destruction of leukocytes and not as a consequence of their redistribution. When rabbits are cooled to a rectal temperature of 30-33°, there is a reduction in the number of thrombocytes and a shortening of blood coagulation time. T. Ya. Ar'yev found that in the case of general cooling of an organism, all the way to a lethal outcome, there is no clearly pronounced change in the osmotic resistance of the erythrocytes, their number, or the hemoglobin content. However, the erythrocyte precipitation reaction is accelerated. In studying blood smears, no morphological changes affecting the erythrocytes were found. On the other hand, the leukocyte count in the peripheral blood showed a considerable increase, evidently due to leukocyte redistribution. Ye. V. Maystrakh also observed leukocytosis with reversible cooling under evipan. /26

In the laboratory of P. M. Starkov (P. M. Starkov, 1968), the role of the direct influence of the cold factor (cooled blood) was demonstrated in the disruption mechanism of the activity of certain brain centers and the parameters of the total bioelectrical activity. These experiments were performed on waking and anesthetized (hexanal) dogs. Hypothermia was achieved by passing the blood from the right carotid artery through a coil submerged in a bath containing water and ice. The cold blood was returned to the external jugular or the peripheral branch of the common carotid artery. It should be pointed

out that during hypothermia produced by returning cooled blood to the peripheral branch of the carotid artery, very early death of the animals results. When the blood is cooled by submerging the "anastomosis" between the carotid artery and the femoral vein in cold water, the animals die at lower body temperatures (21-23°).

In the case of hypothermia produced by cooling, in the coil, the blood located between the artery and the vein, there is an initial brief rise in blood pressure of 30-40 mm Hg. Later, together with a decrease in body temperature, there is a gradual drop in arterial pressure reaching 60-70 mm Hg at 25-24°.

Respiration gradually slowed down as hypothermia increased. The rate of blood flow with an initial drop in body temperature by 1-3° increased and subsequently showed a progressive decline. At body temperatures of 25-24°, the circulation time of the blood was 180-200% of the initial value as a rule.

Hence, if the cooled blood enters the peripheral branch of the carotid artery, i.e., if it is directed straight into the central nervous system, there is an immediate depressor reaction which later is made more severe by the development of acute hypotonia. At a body temperature of 28°, death of the experimental dogs occurs as a result of cardiac arrest. The pressor reaction typical of the first stage of hypothermia is absent, with its characteristic acceleration of the blood circulation rate, which must be viewed as compensatory. In experiments in which the anastomosis was located between the artery and the vein, the phase shifts that were observed were located as a rule in the hemodynamics with an initial rise in blood pressure and a speeding up of the blood flow rate.

No answer has yet been provided to the question of whether the cooled blood exerts a direct influence on the central nervous system as the hypothermal state is developing. Measures of blood temperature by special electrothermometers have shown that its temperature during the first 10-45 seconds drops by 0.3-0.5° and later, over a 15-minute period, by 1.5-2°. Such variations in blood temperature with direct access of the blood into the brain are indicative of a functional state of the central nervous system and e especially the excitability of the vitally important centers and consequently, on the level of the arterial pressure, the rate of blood flow and respiration.

One is struck by the more pronounced inhibition of the vasomotor center as compared to the respiratory center, which is seen not only in the stages of mild hypothermia but also prior to death from cooling.

The different nature of the change in excitability of these centers is seen during hypothermia caused by cooling the blood as it flows into the external femoral vein. The initially insignificant supercooling is accompanied /26
by a regular rise in the excitability of the respiratory and vascular centers. The phase of increased excitability lasts even when the body temperature drops by 1.2°. Subsequently, as a rule, the excitability of the vasomotor center drops significantly while that of the respiratory center continues to rise. This phase, at body temperatures of 30° or less, is followed by a phase of

acute inhibition of the centers in the medulla oblongata. Before death, administration of lobeline is not accompanied by a visible respiration or pressure reaction. Consequently, using this method of supercooling three stages, or phases, can be seen in the change in the excitability of the centers of the medulla oblongata. In the first stage there is an increase in excitability; the second is accompanied by a rise in the excitability of certain sections of the nervous system and inhibition of others while in the third their decline of excitability of all parts of the central nervous system can be seen.

The nature of the change in the excitability of the sympathetic and parasympathetic nervous systems is also a function of the method by which hypothermia is induced. In those cases when the cooled blood is fed directly into the brain, the excitability of the adrenoreactive and cholinoreactive structures decreases progressively, reflected in a drop in the vascular responses to adrenaline and especially pilocarpine. These data correspond to the results of a study of the content of catecholamines in the tissues with isolated cooling of the head. The effect of cold upon the brain through the external coverings of the skull produces more profound changes: exhaustion of noradrenaline resources and a sharp increase in the adrenaline level. In experiments in which the supercooled blood was fed into the enous system with an initial drop in body temperature, there is an increase in the excitability of the vegetative nervous system. Later, a phase develops in which the excitability of the parasympathetic system drops and that of the sympathetic system remains high. This phase of disintegration is quite distinct with a decrease in body temperature by 2-3 or even 4-5°.

Subsequently, the level of both the pressor and the depressor reactions gradually decreases.

Hence, in the mechanism of development of hypothermia by administration of cooled blood into the vein, the influence on the thermoreceptors is of primary importance, followed by the direct action on the central nervous system. This takes the form of a decrease in excitability of the central nervous formations. This view is supported by the results of experiments using electrophysiological methods of research. It has been found that during the first few minutes following cooling of the blood significant changes occur involving the bioelectric activity of the hypothalamus and the cerebral cortex. While the cooled blood returns to the peripheral branch of the carotid artery, i.e., directly influencing the central nervous system, there is an immediate and pronounced desynchronization with a significant decrease in the amplitude of the bioelectrical potentials of the brain structures under study.

Consequently, decreasing the temperature of the blood even by 0.5° is a factor which has a significant influence upon the functional state of the central nervous system and has a direct influence on the brain. A further decrease in body temperature is accompanied by a still greater inhibition of bioelectrical activity.

Warming

Here, the data indicate that up to certain temperatures hypothermia does not cause organic damage incompatible with life, but promotes extreme inhibition of the functions of organs and systems. Consequently, there is a real possibility of recovery of vital activity in the course of reverse heating. These problems are discussed in more detail in the previous section of the present chapter. We will merely mention that at the present time rapid heating of the cooled individuals is considered to be most advisable. In the opinion of the supporters of this method, the possibility of intensifying metabolic changes is reduced. However, there are equally good bases for assuming that massive heating can have serious consequences. B. V. Petrovskiy, G. M. Solov'yev and A. A. Bunatyan (1967), based on their survey of a great deal of clinical experience with hypothermal perfusion, consider one of the possible shortcomings of this method to be the development of a significant temperature gradient between the various organs and tissues -- the development of "patchy" metabolism. Such a phenomenon in the final analysis causes decompensation of metabolic acidosis, i.e., one of the basic factors of the "irreversibility" of the process. The latter is correlated with the high level of adrenalinemia in rapidly-heated victims, making the peripheral spasm symptoms more pronounced, as well as those of generalized hypoxia and metabolic acidosis. On this basis the authors recommend "stepwise" heating, creating the prerequisites of a development of optimum conditions of adequate blood supply not only to the vital organs but also to the peripheral tissues which are the principal source of metabolic acidosis in hypothermal perfusions. /26

Conclusions

The damaging influence of the cold factor creates a qualitatively new condition in the organisms of homothermal animals and man; this state is referred to as hypothermal. The drop in body temperature is the result of disruption of heat regulation. In the course of their phylogenetic development, homothermal animals have developed a complicated system of accommodating reactions which enable them to retain normal body temperature for a certain period of time when exposed to cold. The initial reaction to cooling is activation of the entire system of neuroendocrine regulation, resulting in a stepping up of metabolism and thus of heat generation. At the same time, heat loss is limited, primarily because the peripheral vessels contract. These reactions are aimed at maintaining the temperature limit specific to a given species when the ambient temperature drops significantly.

The drop in body temperature reflects the ability of the compensatory processes and is accompanied by a restructuring of the organism's vital activity at a new level according to the degree of the hypothermia which develops. Inhibition of the cerebral cortex, and subsequently the vegetative centers of the brain, causes metabolic and trophic functions to be inhibited. A sharp decrease in energy expenditure makes it possible for the organism to exist in a state of hypothermia. An important part in the formation of functional changes under the harmful effects of cold is played by a powerful flow of extero- and interoreceptive impulsation, and later by the direct influence of cooled blood. /26

The changes in organ and system activity caused by deep cooling are reversible to a certain extent. It is considered that the specific functions of various organs cease at different temperature levels, referred to as "biological zero". Death during hypothermia usually results from primary stoppage of respiration against a background of inhibition of the bulbar centers.

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